

PHARMACOGENETIC TESTING IN OUTPATIENT MENTAL HEALTH CLINICS

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at the University of Missouri-Columbia

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Doctor of Philosophy

by

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The undersigned, appointed by the dean of the Graduate School, have examined the dissertation entitled

PHARMACOGENETIC TESTING IN OUTPATIENT MENTAL HEALTH CLINICS

presented by Tammie Gainey,

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DEDICATION

I would first like to dedicate my work to my husband who has stood by my side and encouraged me every step of the way. I couldn't have completed this work without his support.

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PHARMACOGENETIC TESTING IN OUTPATIENT MENTAL HEALTH CLINICS

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ABSTRACT

The purpose of this study was to evaluate mental health clinicians' perceived knowledge regarding pharmacogenetic testing; their attitude, receptivity towards, and confidence in pharmacogenetic testing; and how pharmacogenetic testing is being implemented to support decision making in outpatient clinics. This study was guided by Rogers' Diffusion of Innovation (DOI) Theory. An exhausted literature search was conducted to find studies on mental health clinicians' knowledge, perceived attitudes, and implementation of pharmacogenetic testing. The subject population included 28 mental health clinicians who are actively utilizing pharmacogenetic testing in outpatient mental health clinics. Participants responded to semi-structured open-ended prompts regarding knowledge, perceptions and implementation of pharmacogenetic testing in mental health outpatient clinics. Data were analyzed using a qualitative descriptive approach. Five relevant themes emerged related to the perceptions of pharmacogenetic testing, impact on clinical decision-making, associated concerns of pharmacogenetic testing, knowledge gaps among clinicians, and policy challenges. Overall, clinicians perceived pharmacogenetic testing beneficial to guide dosing and medication selection to decrease the risk of side effects and increase tolerability of psychotropic medications. This study will lead to future research to support shared decision-making around pharmacogenetic testing, medication adherence and tolerability, and setting guidelines for pharmacogenetic testing in mental health clinics.

Chapter I

Introduction

Approximately 100,000 deaths occur annually in the U.S. due to adverse effects from medications (Davies, Green, Taylor, Williamson, Mottram, & Pirmohamed, 2009; Eichelbaum, Ingelman-Sundberg, & Evans, 2006). Pharmacogenetics is the phenomenon where an individual's gene variations influence drug response and side effects (Lohaff & Ferraro, 2010). Pharmacogenetic testing focuses on a single gene and drug interaction and supports the adoption of precision medicine in mental health (Hess, Fonseca, Scott, & Fagerness, 2015; Schosser & Kasper, 2009). Precision medicine is defined as treatments tailored to meet individual's needs using genetic information (Jameson & Longo, 2015). Clinicians are increasingly using such testing to guide medication selection and dosing to improve patient outcomes (National Institutes of Health: National Human Genome Research Institute, 2014).

Although pharmacogenetic testing has been used in oncology, cardiology and pain management, it is only beginning to be used in outpatient mental health settings. Pharmacogenetic testing has the potential to identify genetic differences in medication response and guide clinical decision making. This study begins to address the gap regarding knowledge, attitudes, and practices of mental health clinicians regarding pharmacogenetic testing, an intervention with significant future implications for treatment decision-making.

The tolerability and effectiveness of psychotropic medications is highly variable. Approximately 60% of patients do not respond completely to antidepressants and 30% do not respond at all (Crisafulli et al., 2011). Similarly, 74% of patients being treated for

Schizophrenia discontinued medications due to side effects and ineffectiveness (Lieberman et al., 2005). Due to genetic factors, patients may vary widely in how they respond to mental health medications. For example, genetic factors contribute to approximately 50% of antidepressant responses (Crissafull et al., 2011). Patients metabolize antidepressants at vastly different rates and can experience different responses to the same drug (Dalen, Dahl, Ruiz, Nordin, & Bertilsson, 1998; Lohaff & Ferraro, 2010).

According to the Food and Drug Administration, there are more than 100 prescription medications that have pharmacogenetic information while approximately 30% are psychotropic medications (Food and Drug Administration, 2015; Malik, Caley, & Azeem, 2014). A large percentage of psychotropic medications are metabolized by the CYP450 enzyme system: 1A2, 2B6, 2C9, 2D6, and 3A4 (Black, O’Kane, & Mrazek, 2007). A patient’s metabolizer status can be determined according to the enzyme. Patients may be ultra-rapid metabolizers, extensive metabolizers, intermediate metabolizers, or poor metabolizers of a certain medication – requiring very different doses or perhaps different medications-- depending on their genetic expression of a particular enzyme. An ultra-rapid metabolizer refers to someone whose metabolic capacity is greater than normal and will likely require a higher dosage of medications to obtain the same response as someone who is an extensive metabolizer. An extensive metabolizer represents a person with a normal metabolic capacity who requires standard doses of medications to obtain a therapeutic response. An intermediate metabolizer refers to a person with a decreased metabolic capacity requiring lower doses of medications to decrease the risk of side effects and increase efficacy of medications. A poor metabolizer

represents an absent metabolic capacity, which at standard doses patients are at increased risk of accumulation of medication, side effects and decreased efficacy of the medication (Black et al., 2007).

Among patients with mental illness, side effects and decreased efficacy of antidepressants and antipsychotics result in substandard outcomes, medication nonadherence, and loss of confidence in medications (Mulsant & Lenze, 2014). Pharmacogenetic testing may provide safer and more effective treatments among patients with mental illness (Walden et al., 2015). The utilization of pharmacogenetic testing in medication selection and dosing has resulted in patients with earlier remission in treatment (Smits, Smits, Schouten, Peeters, & Prins, 2007).

Many mental health clinicians report positive attitudes towards pharmacogenetic testing (Haga Burke, Ginsburg, Mills, & Agans, 2012; Lankree, et al., 2014; Mrazek et al., 2007). Large majorities of psychiatrists and general practitioners surveyed in research believe pharmacogenetic testing would be beneficial to guide medication selection among patients with mental illness (Thompson, Hamilton, & Hippman, 2015) and will become a standard of care (Walden et al., 2015). The use of pharmacogenetic testing has doubled from 2012 to 2015 and clinicians believe that it will continue to rapidly increase over the next few years (Walden et al., 2015).

Research consistently shows clinicians typically report limited knowledge or understanding of pharmacogenetic testing (Dodson 2011; Kadafour, Haugh, Posin, Kayser, & Shin, 2009; Hoop, Lapid, Pualson, and Roberts, 2010, Dodson & Lewallen, 2011, Tamaoiki, Gushima, & Tsutani, 2007). Many also report concerns regarding cost effectiveness, ethical concerns, lack of medication adherence, patient acceptability, time

frame of test, and inadequate evidence-based outcomes (Dorfman, Trinidad, Morales, Howlett, Burke, & Woodahl, 2014; Ghaddar, Cascorbi, & Zgheib, 2012; Haga, Tindall, & O'Daniel, 2012; Schnoll & Schields, 2011; Squassina et al., 2010). No guidelines exist to guide mental health clinicians in the use of pharmacogenetic testing in clinical practice (Quinones et al., 2014) and very little is understood about how mental health clinicians understand and implement such tests in outpatient settings.

Rogers' Diffusion of Innovation (DOI) theory (Rogers, 2003) guides the proposed study. DOI theory suggests innovation adoption involves five stages: knowledge, persuasion, decision, implementation, and confirmation. This study will focus on mental health clinicians' knowledge, beliefs and opinions, decision making, and the implementation of pharmacogenetic testing in mental health clinics. Identifying how pharmacogenetic testing is being implemented in current practice and how it affects treatment decision making may have a positive effect on reducing unwarranted adverse effects while enhancing the effectiveness and tolerability of psychotropic medications. To assist mental health clinicians in understanding pharmacogenetics, the knowledge and beliefs of pharmacogenetic testing among mental health clinicians must be identified.

This study will contribute to the literature by exploring the knowledge, beliefs, and implementation strategies of pharmacogenetic testing among mental health clinicians in outpatient mental health clinics. Qualitative analysis can help identify knowledge gaps and reveal challenges in implementation of pharmacogenetic testing. This study will use a qualitative descriptive approach to address this gap and describe mental health clinicians' adoption of pharmacogenetic testing and how such testing is being implemented into clinical workflow to support clinical decision making.

A greater understanding of the utilization of pharmacogenetic testing in medication management may reduce serious adverse effects and polypharmacy which are common in mental health prescribing (Laje, 2013). Pharmacogenetic testing can determine if patients are experiencing multiple side effects or an ineffective dose response due to their metabolizer status (Kung & Xiaofan, 2010). Pharmacogenetic-guided treatment can improve the accuracy of medication responses and decrease the risk of side effects (Mrazek et al., 2010).

This research has important implications for future advanced nursing practice and precision medicine around pharmacogenetic testing and medications (e.g., examining patient perspectives and testing influence on outcomes such as decision conflict, medication adherence, and illness trajectories) and intervention development (e.g., patient decision aids) among patients with mental illness (Substance Abuse and Mental Health Services Administration, 2010). Disseminating information about knowledge gaps regarding pharmacogenetic testing among mental health clinicians may aid in the implementation of pharmacogenetics in nursing and medical curricula. In addition, this knowledge may assist in the development of continuing education for practicing mental health clinicians.

Chapter II

Review of Related Literature

This chapter reviews the history of pharmacogenetic testing and prescribing in mental health. In addition, this chapter reviews previous literature and describes search methods and results. A review of mental health clinicians' knowledge, perceived attitudes, and implementation of pharmacogenetic testing is included in this section. Lastly, this chapter describes Roger's Diffusion of Innovation Model and how this model will guide the study.

History of Pharmacogenetic Testing in Mental Health

In 2003, the Human Genome Project was successful in mapping the first human genome (National Institute of General Medical Sciences, 2013). Genome is defined as the complete set of instructions found in a cell (National Institutes of Health U.S. National Library of Medicine, 2017). Pharmacogenetics is how a person's genome influences the metabolism of certain medications (National Institute of General Medical Sciences, 2013).

There are more than 3 billion DNA base pairs in the copy of a person's genome (National Institutes of Health U.S. National Library of Medicine, 2017). A person's DNA determines how cytochrome P450 enzymes affect medication metabolism. Although there are over 50 variations of enzymes, approximately 90% of medication metabolism is affected by only six CYP450 enzymes (Lynch & Price, 2007). A large percentage of psychotropic medications are metabolized by the following CYP450 enzymes: CYP1A2, CYP2B6, CYP2C9, CYP2D6, and CYP3A4 (Black, O'Kane, & Mrazek, 2007).

Among the CYP450 enzymes, CYP2D6 and CYP2C19 are involved in many antidepressants and antipsychotics (PharmGKB, 2015). Researchers found in a retrospective study that hospitalized psychiatric patients with one or two nonfunctioning CYP2D6 alleles prescribed antidepressants or antipsychotics were more likely to have medication changes (Mulder et al., 2005). Alleles are one of two versions of a gene that affects inherited traits (Quigley, 2015). Each person inherits one allele from each parent which means that there are two alleles for each gene (Quigley, 2015). Patients with nonfunctioning CYP2D6 or CYP2C19 enzymes have resulted in longer hospitalizations (Kropp, Lichtinghagen, Winterstein, Schlimme, & Schneider, 2006). In another retrospective study, researchers found patients who were poor metabolizers of CYP2D6 resulted in longer hospitalizations if taking psychotropics dependent on the enzyme CYP2D6 for metabolism (Chou et al., 2000). Patients identified as ultra-rapid metabolizers were found to have lower blood levels of tricyclic antidepressants resulting in nonadherence to medications (Kootstra-Ros et al., 2006). Variants in genes may affect the efficacy and toxicity of medications.

Although traditional treatment focuses on a trial and error approach, pharmacogenetic testing may be used to guide treatment decisions regarding medication selection and dosing to predict and reduce adverse reactions and efficacy of medications (Dahl & Sjoqvist, 2000; Langman & Dasgupta, 2012). A trial and error approach increases the risk of side effects, being over medicated, or the medication being ineffective to treat symptoms (Mrazek, 2010). This method of prescribing often delays the alleviation of symptoms due to an increase lag time in medication response taking weeks to months to find the right medication (Crettol, de Leon, Hiemke, & Eap, 2014).

Currently, there are thirteen commercial pharmacogenetic tests available in the United States for psychotropic medications (Bousman & Hopwood, 2016). GeneSight and Genecept are both pharmacogenetic tests that have demonstrated clinical usefulness in clinical trials in the United States (Bousman & Hopwood, 2016). Pharmacogenetic testing requires genotyping, either buccal or blood, to obtain a DNA sample (Ng, Schweitzer, Norman, & Easteal, 2004). This single DNA test is one time test since a person's genetic variations do not change during a person's lifetime (Ng et al., 2004).

Since 2004, pharmacogenetic testing has been used in academic and tertiary medical centers to guide treatment among patients with mental illness, however, such testing has not been used routinely in outpatient mental health practice (Hall-Flavin, Schneekloth, & Allen, 2010; Mrazek, 2010). More recently there has been a rapid expansion of pharmacogenetic testing in outpatient mental health settings (Brennan, 2015). Unfortunately, many mental health providers are unfamiliar with such testing (Bousman & Hopwood, 2016).

Previous Literature

Previous reviews of literature have focused on challenges for precision medicine in psychiatry, implications of pharmacogenetic testing in psychiatry, application of pharmacogenetics in mental health prescribing (Burke, Love, Jones, & Fife, 2016; Dalvie et al., 2016; Ng, Schweitzer, Norman, & Easteal, 2004). Additional literature reviews have focused on stakeholders' views of pharmacogenetic testing and knowledge and attitudes of pharmacogenomics among healthcare professionals (Dodson, 2011; Patel, Ursan, Zueger, Cavallari, & Pickard, 2014). The latter two literature reviews do not have a specific emphasis on psychiatry but rather focus on healthcare professionals, general

public, patients, and payers (e.g., insurance companies and hospitals) (Dodson, 2011; Patel et al., 2014). This review will focus on mental health clinicians and pharmacogenetic testing.

Search Methods

A review of articles published from 2004 to 2017 was conducted on mental health clinicians' knowledge, perceived attitudes, and implementation of pharmacogenetic testing. Pharmacogenetic testing was initially utilized to guide treatment among patients with mental illness in 2004, therefore the author chose to search the literature beginning in 2004 (Hall-Flavin, Schneekloth, & Allen, 2010; Mrazek, 2010). A search was conducted using PubMed/Medline, CINAHL, PsycInfo, and Academic Search Complete databases. The following terms were utilized in a multi-search field: pharmacogenetics, personalized medicine, precision medicine, healthcare professionals, perceptions, attitudes, opinions, psychiatry, and mental health. Studies were included if the sample consisted of psychiatrists or other mental health clinicians (e.g., advanced practice nurses, physician assistants, and medical students in psychiatry).

Search Results

The literature search yielded 97 relevant articles on mental health clinicians' knowledge, perceived attitudes, and implementation of pharmacogenetic testing. Titles and abstracts were reviewed and articles that did not meet inclusion criteria were eliminated. Studies were excluded if one of the following occurred: sample included only non-mental health clinicians and interventions other than pharmacogenetic testing to guide treatment among patients with mental illness. There were eight relevant articles published from 2004 to 2017, see Table 1. The majority of the studies were quantitative

survey design while only one study was a mixed methods design and one study was a qualitative design. Most studies focused on psychiatrists or psychiatry residents.

Table 1. Overview of Relevant Studies

Author (year)	Design	Sample	Knowledge	Opinions & Perceptions	Implementation
Dunbar, Butler, Wheeler, Pulford, Miles, & Sheridan (2012)	Qualitative	Total n=33 Mental Health Clinicians Public Mental Health Services of three District Health Boards in New Zealand.	n/a	<p>Perceived Usefulness Confirmed prior clinical decisions judgement regarding dosing.</p> <p>Explained why patients may have increased sensitivity to medications.</p> <p>Built a level of trust and rapport with the patients.</p> <p>Advantages: Determine the dose with the least amount of side effects.</p> <p>An indicator for starting dose of medications.</p> <p>Predict fewer side effects.</p> <p>Greater medication adherence.</p>	<p>Ordering and Receiving of Pharmacogenetic Test (AmpliChip CYP450) Advantages: Forms were straightforward and simple to complete.</p> <p>Disadvantages: Laboratory staff unfamiliar with test requiring additional blood samples from patient.</p> <p>Delay in receiving results (average 8 days).</p> <p>Poor accessibility of test forms and lack of awareness of study end date.</p> <p>Reasons for not ordering test: Patient was discharged or did not return for service.</p>

Table 1. Continued

Author (year)	Design	Sample	Knowledge	Opinions & Perceptions	Implementation
Dunbar, Butler, Wheeler, Pulford, Miles, & Sheridan (2012) <i>(continued)</i>			n/a	<p>Clinicians more confident in dosing decisions.</p> <p>Greater utility for patients who were “abnormal metabolizers” and at risk of side effects at low doses of medications.</p> <p>Potential Disadvantages: Clinicians focus on the blood test instead of the patient.</p> <p>Cost of test.</p> <p>Additional paperwork for provider.</p> <p>Delays in receiving results.</p> <p>Increased anxiety for patients due to process.</p>	<p>Setting required immediate treatment and delay in results.</p> <p>Medication was stopped prior to obtaining test results.</p> <p>Patient was not experiencing side effects.</p> <p>Clinician unsure how to utilize the test results.</p>

Table 1. Continued

Author (year)	Design	Sample	Knowledge	Opinions & Perceptions	Implementation
Finn, Wilcox, Korf, Blacker, Racette, Sklar, & Smoller (2005)	Quantitative	<p>Total n=352 Psychiatrists</p> <p>Attending a continuing education medical education course, 97% of participants from the United States or Canada.</p>	<p>Less than 25% perceive themselves as competent to discuss genetic information regarding genetic testing with patients and families.</p> <p>87% routinely ask detailed family history of psychiatric illness during evaluation.</p> <p>40% of respondents stated that current medical literature was primary source of genetic information.</p> <p>27% from courses in medical training or clinical training</p> <p>22% from CME courses</p>	83% believe that it is their role to discuss genetic information with patients and families.	n/a

Table 1. Continued

Author (year)	Design	Sample	Knowledge	Opinions & Perceptions	Implementation
Finn, Wilcox, Korf, Blacker, Racette, Sklar, & Smoller (2005) <i>(continued)</i>			7% from informal consultation with colleagues 1% popular press or media 3% other		
			Respondents expressed further interest in genetic education: Written education materials (93%), CME courses (82%), Web/Internet Resources (81%), Multidisciplinary consultation with colleagues (77%).		
Hoop, Lapid, Paulson, & Roberts (2008)	Quantitative	Total n=45 Psychiatrist chosen randomly from the American Medical Association Masterfile.	No respondents referred patients for genetic consultation for psychiatric illness in the past year (n=43).	78% of respondents believe psychiatrist should be the one to provide genetic counseling to patients.	

Table 1. Continued

Author (year)	Design	Sample	Knowledge	Opinions & Perceptions	Implementation
Hoop, Lapid, Paulson, & Roberts (2010)	Mixed Methods	Total n=75 Residents and Faculty In 3 Departments of Psychiatry Academic Centers in the United States—Mayo Clinic, University of Louisville, & Georgia Medical College	Training Received (n=67) None: 5% Minimal: 56% Moderate: 21% Extensive: 5% Experience (n=59) (mean, SD) Ordered PGT in past 12 months (20.86, 48.5) 14.7% did not order PGT in past 12 months. 64% ordered testing 1 or more times in past 12 months.	79% respondents did not order genetic test in past 5 years (n=42). Perceived Usefulness (n=64) (mean, SD) Medication tolerance (3.66, 0.59) Treatment-resistance Depression (3.60, 0.70) Chronic Schizophrenia (2.98, 0.86) Perceived Risks (n=36) (mean, SD) Provide secondary information about susceptibility to disease or prognosis (2.89,	Genetics has an influence on overall mental health (mean, SD) (3.64, 0.48) Practices when Ordering PGT (x², p-value) Inform patients test is being ordered (0.00, 1.000) Obtain patient's verbal consent (0.22, .642) Inform about cost of test (1.57, .211) Test only patients if there is an immediate medical benefit (0.061, .804) Test only patients with decisional capacity (0.005, .942)

Table 1. Continued

Author (year)	Design	Sample	Knowledge	Opinions & Perceptions	Implementation
Hoop, Lapid, Paulson, & Roberts (2010) (continued)				0.53) Cause a Patient Psychological Distress (2.85, 0.58)	Test patients who unlikely will have benefit but may gain information for future (.764, .382)
				Perceived Ethical Concerns (n=66) (mean, SD)	Test only patients over 18 (0.09, .0764)
				Ensure confidentiality of Results (3.35, 0.54)	Practices when Receiving PGT Results
				Competence in Interpretation of Results (3.30, 0.58)	Meet with patients to answer questions and explain results (0.43, .514)
				Obtain Informed Consent Prior to test (3.29, 0.63)	File results in patients' medical record (4.68, <.05)
				Pretest and Posttest counseling (3.20, 0.66)	Tell patients that results may pertain to other family members (3.05,

Table 1. Continued

Author (year)	Design	Sample	Knowledge	Opinions & Perceptions	Implementation	
Hoop, Lapid, Paulson, & Roberts (2010) <i>(continued)</i>				Provide test if benefits outweigh risks (3.05, 0.51)	.081)	
				Provide test only to patients with decision making capacity (2.70, 0.80)	Communicate results to the patient's primary doctor (0.001, .979)	
					Perceived Professional Impact (mean)	Tell patients that results may provide secondary information (5.24, <.05)
					Psychiatric Patients would benefit from PGT (3.03)	Create a separate file for test results kept apart from official medical record (4.56, <.05)
					PGT would Dramatically change the practice of psychiatry (2.77)	
				PGT too expensive for patients (2.60) (neither agreed or disagreed)		
				Five Dominant		

Table 1. Continued

Author (year)	Design	Sample	Knowledge	Opinions & Perceptions	Implementation
Hoop, Lapid, Paulson, & Roberts (2010) <i>(continued)</i>				<p>Themes from Qualitative Analysis: (n=17) Optimism about the potential of psycho-pharmacogenetic testing.</p> <p>Dismissal of concerns about risks of testing.</p> <p>Identification of barriers to widespread clinical testing.</p> <p>General skepticism about current benefits of testing.</p> <p>Concerns that testing is being used inappropriately.</p>	
Lanktree, Zai,	Quantitative	Total n=910	Exposure to	90% of	

Table 1. Continued

Author (year)	Design	Sample	Knowledge	Opinions & Perceptions	Implementation
Vanderbeek, Giuffra, Smithson, Kipp, Dalseg, Speechley, & Kennedy (2014)		Undergraduate Medicine and Science Students from the University of Waterloo (n=542), the University of Western Ontario (n=268), and the University of Toronto (n=100).	genetic testing (86%) and mental illness (81%) in the classroom.	respondents support using genetic information when determining medication treatment for patients with Schizophrenia.	
Mrazek, Drought, Koenig, et al. (2007)	Quantitative	<p>Total n=41 Psychiatrists 76.47% Nurse 7.84 % Social Worker 1.96% Psychologist 1.96% Researcher 3.92% Other 7.84%</p> <p>Enrolled in a 5-day course on psychiatric genomics at the Mayo Clinic.</p>		<p>59% of respondents were willing to pay for 2D6 and 2C19 genotyping by the end of the course at the cost of \$375</p> <p>95% would be willing to participate in a research project to receive the test at no cost.</p> <p>98% believed that</p>	

Table 1. Continued

Author (year)	Design	Sample	Knowledge	Opinions & Perceptions	Implementation
Thompson, Hamilton, & Hippman (2015)	Quantitative	<p>Total n=113 Psychiatrists and Psychiatry Residents</p> <p>From UCSF Langley Porter Psychiatric Institute and San Francisco Bay area community.</p>		<p>adults have the right to know their genotypes</p> <p>Perceptions: 96% Believe that genetic information may help with decision making regarding medication in the treatment of psychiatric illnesses.</p>	
Thompson, Hamilton, & Hippman (2015) <i>(continued)</i>				<p>97.3% Would use information if drug-drug interaction was indicated.</p> <p>85.1 % Believe that genetic testing will become standard of care in psychiatric treatment.</p> <p>72.6% Believe that genetic counseling</p>	

Table 1. Continued

Author (year)	Design	Sample	Knowledge	Opinions & Perceptions	Implementation
Walden, Brandl, Changasi, Sturgess, Soibel, Notaro, Cheema, Braganza, Marshe, Freeman, Tiwari, Kennedy, & Muller (2015)	Quantitative	Total n=168 Psychiatrists (33.9%, n=57) Clinician Scientists (7.1%, n=12) General Practitioners (40.5%, n=68) Other specialties (18.5%, n=31) From the Centre for Addiction and Mental Health in Toronto, Canada.		<p>would be beneficial to discuss genetic test results.</p> <p>Perceptions: (mean, SD) Clinician scientists were more favorable of test than psychiatrist ($p < 0.05$).</p> <p>80% of physicians believed pharmacogenetic testing would become standard of care in psychiatric treatment.</p>	<p>Practices when ordering Pharmacogenetic Testing (TaqMan Assays):</p> <p>Obtain blood sample</p> <p>48 hour turn-around time for genotyping</p>

Mental Health Clinicians' Knowledge of Pharmacogenetic Testing

Very little education is received by clinicians on pharmacogenetics in traditional medical programs (Gershon, Alliey-Rodriguez, & Grennan, 2014). Approximately 60% of physicians believe that only specialists have knowledge and understanding about pharmacogenetic testing (Tamaoiki, Gushima, & Tsutani, 2007). According to Collins (1999) most clinicians have received less than one hour of instruction on pharmacogenetics. Researchers found that clinicians have made errors in translating pharmacogenetic testing results to patients due to lack of knowledge (Giardello et al., 1997).

Research consistently shows clinicians typically report limited knowledge or understanding of pharmacogenetic testing. From a systematic review, Dodson (2011) found that five out of six articles confirmed that healthcare providers had limited knowledge on pharmacogenetic testing. However, only one of the six articles from Dodson's (2011) systematic review looked at mental health clinicians' knowledge on pharmacogenetic testing (e.g., psychiatry attending physicians and psychiatry residents) (Hoop, Lapid, Pualson, & Roberts, 2010).

Hoop et al., (2010) found that among a sample of 75 psychiatric faculty and residents, 61% had none to minimal training of pharmacogenetic testing while 26% had moderate to extensive training in pharmacogenetic testing. However, the study was conducted at three academic medical centers which were early adopters of pharmacogenetic testing. Therefore, the amount of training received may be larger than among outpatient psychiatrists (Hoop et al., 2010). Researchers assessed psychiatric faculty and residents' (n=67) competency level based on the following five items: belief

that it is a psychiatrist's role to offer pharmacogenetic testing in appropriate clinical circumstances, order pharmacogenetic tests, identify clinical situations in which testing is indicated, inform patients of risks and benefits of testing, and make treatment recommendations based on results (Hoop et al., 2010). Participants were asked to rate their level of agreement on a scale of 1 to 5, 1 being strongly disagree and 5 being strongly agree. Participants with moderate to extensive training (mean = 3.38) rated themselves as more competent when compared to those with none to minimal training (mean 2.63) [$F_{1,63} = 49.78, p < .001$]. In addition, participants who have utilized pharmacogenetic testing in practice within the last 12 months (mean = 2.96) rated themselves as more competent than those who had not ordered pharmacogenetic testing (mean = 2.36) [$F_{1,56} = 16.33, p < .001$] (Hoop et al., 2010).

Two additional studies focused on mental health clinicians' knowledge of genetics and the likelihood of developing a mental illness (Finn et al., 2005; Hoop, Roberts, Hammond, & Cox, 2008). In a quantitative study, the majority of psychiatrists (60%) had not had recent genetic training within the past five years (Hoop et al., 2008). Respondents who had obtained genetic training in the in past 5 years had more experience with providing genetic testing (Hoop et al., 2008). However, 70% of psychiatrists felt competent to interpret genetic test results to patients regarding psychiatric illness. Many psychiatrists believed that their medical training prepared them for genetic counseling (Hoop et al., 2008).

In contrast, fewer than 25% of psychiatrists or psychiatrists in training (n=352) attending a continuing medical education course felt competent to discuss genetic information with patients and families (Finn et al., 2005). The majority of respondents

(40%) stated that their primary source of genetic information was obtained from the current medical literature. Additional respondents obtained educational resources on genetic information from medical or clinical training (27%), CME courses (22%), informal consultation with colleagues (7%), popular press or media (1%), or other (3%). Most respondents were interested in further genetic education via written education materials (93%), CME courses (82%), Web/Internet resources (81%), and multidisciplinary consultation with colleagues (77%) (Finn et al., 2005). Although these two studies focused on psychiatrists' knowledge of genetics, this study did not assess knowledge of pharmacogenetics specifically.

A sample of undergraduate medicine and science students (n=910) from three different universities, University of Waterloo (n=542), University of Western Ontario (n=268), and University of Toronto (n=100), completed questionnaires on pharmacogenetic testing for psychotropic medications (Lanktree et al., 2014). The majority of the respondents received information on genetic testing (86%) and mental illness (81%) in the classroom and believed that such testing should be utilized to determine which medication to prescribe (Lanktree et al., 2014). However, the knowledge of pharmacogenetic testing among the general public is less prevalent (Wilde, Meiser, Mitchell, & Schofield 2010).

To the author's knowledge, no additional studies have assessed mental health clinicians' knowledge of pharmacogenetic testing. Additional studies have focused on nursing students and other healthcare professionals (Dodson, 2014; Dodson & LeWallen, 2011; Haga, Burke, Ginsburg, Mills, & Agans, 2012; Kadafour et al., 2009; Kudzi, Addy, & Dzudzor, 2015; Selkirk, Weissman, Anderson, & Hulick, 2013; Stanek et al., 2012).

The majority of studies have focused on general practitioners, pharmacists, and nurses (Haga et al., 2012; Kadafour et al., 2009; Selkirk et al., 2013; Stanek et al., 2011).

Two studies focused on oncology nurses' and undergraduate student nurses' knowledge of pharmacogenetics (Dodson, 2014; Dodson & Lewallen, 2011). Among oncology nurses (n=368) 72 % perceived they had fair to poor knowledge of pharmacogenetics. Only three out of 368 oncology nurses were nurse practitioners (Dodson, 2014). Participants had greater knowledge of pharmacogenomics (mean = 2.45; SD = 1.4) when compared to genomic knowledge (mean = 2.62 SD = 1.44). Overall, nurses with previous experience with pharmacogenetic testing had greater knowledge (Dodson, 2014). Additional researchers found that among 275 undergraduate nursing students, 76% reported minimal to no knowledge of pharmacogenetics (Dodson & Lewallen, 2011).

Four additional studies focused on other healthcare professionals and their knowledge level of pharmacogenetic testing in clinical practice (Haga et al., 2012; Kadafour et al., 2009; Selkirk et al., 2013; Stanek et al., 2011). Researchers found 66% of healthcare professionals (n=448) had a general lack of knowledge of pharmacogenetics (Kadafour et al., 2009). The sample included pharmacists (n=268), nurses (n=102), physicians (n=52), physician assistants (n=5), and other healthcare professionals (n=3). Participants who had pharmacogenetic testing available at their workplace had more knowledge of pharmacogenetics. However, there was not a difference in knowledge between pharmacists and nurses (Kadafour et al., 2009).

Similarly, among a multidisciplinary group of physicians (n=249) (e.g., geneticists, internists, vascular surgeons, and oncologists), there is a general lack of

knowledge about genomics (73%) (Selkirk et al., 2013). Only 11.2% of physicians reported using pharmacogenetic testing in practice. A major barrier was the time required to stay abreast of knowledge of pharmacogenetics and latest advances in practice (70%) (Selkirk et al., 2013).

Additional researchers found that 52.4% of family medicine and internal medicine physicians (n=597) were not knowledgeable about genetic testing (Haga et al., 2012). Among respondents, 32% had never ordered genetic testing and 38.7% were not comfortable ordering such testing. Many respondents had heard of pharmacogenetic testing through journals (46.9%) or professional meetings (46.61%), but most respondents (79.6%) had never ordered pharmacogenetic testing. However, a large majority of physicians (64.5%) believed that pharmacogenetic testing will soon be valuable to predict adverse events and the effectiveness of medications (Haga et al., 2012).

Researchers found that 97.6% of physicians (n=10,303) were favorable to genetics being influential to a patient's drug response (Stanek et al., 2011). However, only approximately 10% felt competent about pharmacogenetic testing. Early adopters reported more knowledge about the clinical application of the test and had received pharmacogenetics training in medical school (26.3%) or post graduate training (44.2%) (Stanek et al., 2011).

Overall, mental health care clinicians and other healthcare professionals have a generalized lack of knowledge of genetics and pharmacogenetics. Additional assessments of mental health clinician's knowledge are needed among outpatient and inpatient psychiatric providers. Early adopters seem to have more knowledge and understanding

about pharmacogenetics compared to those who have not utilized pharmacogenetic testing in practice. Many clinicians and healthcare professionals believe that pharmacogenetic testing will be valuable. There is a lack of education on pharmacogenetics in nursing and medical curricula. There is an urgency to understand the knowledge of pharmacogenetics testing among mental health clinicians as pharmacogenetic testing expands into outpatient clinics.

Mental Health Clinicians' Perceived Attitudes of Pharmacogenetic Testing

A mental health clinician's perceived attitudes and opinions regarding pharmacogenetic testing is important in understanding the usefulness of such testing in practice. Six out of eight articles discussed mental health clinicians' perceived attitudes regarding pharmacogenetic testing (Dunbar, Butler, Wheeler, Pulford, Miles, & Sheridan, 2012; Hoop et al., 2010; Lanktree et al., 2014; Mrazek et al., 2007; Thompson et al., 2015; Walden et al., 2015). Two additional articles discussed mental health clinicians' perceptions of genetic testing in regards to the likelihood of psychiatric illness (Finn et al., 2005; Hoop et al., 2008).

Perceived usefulness. In several studies, researchers found that mental health clinicians perceived pharmacogenetic testing to be useful in clinical practice regarding medication selection and dosing (Dunbar et al., 2012; Hoop et al., 2010; Lanktree et al., 2014; Thompson et al., 2015). In a qualitative study of mental health clinicians (n=33) in New Zealand, mental health clinicians found the implementation of the AmpliChip CYP450 pharmacogenetic test to be useful in guiding treatment in patients with psychiatric illness (Dunbar et al., 2012). The AmpliChip CYP450 test was approved by the Federal Drug Administration in 2005. The test analyzes a patient's DNA via a blood

sample to determine a patient's phenotype for CYP2D6 and CYP2C19. The majority of patients (71%) were being prescribed antipsychotics for their psychiatric illness (psychotic disorder 55.2%, mood disorders 36.3%, other disorders 8.5%), while approximately 30% were prescribed risperidone versus other antipsychotics (Dunbar et al., 2012).

Researchers found that mental health clinicians reported several benefits of pharmacogenetic testing (Dunbar et al., 2012). First of all, clinicians found the testing to be useful in finding the right target dose and confirmed clinical decisions regarding medication selection and changes made previously, thus making clinicians more confident in their dosing selections. This provided reassurance in dosing changes (Dunbar et al., 2012). In a mixed methods study, Hoop et al. (2010) found that the majority of psychiatrist's and residents in psychiatry (n=65) perceived pharmacogenetic testing most useful in medication tolerance (mean = 3.66, SD = 0.59) and treatment-resistance depression (mean = 3.60, SD = 0.70). Participant responses were on a scale from 1 (not useful) to 4 (extremely useful).

Similarly, other psychiatrists and residents in psychiatry (n=113, 96%) believe that pharmacogenetic testing may help in the decision-making process when treating patients with psychiatric illness (Thompson et al., 2015). In addition, 90% of undergraduate medicine and science students (n=910) positively supported using genetic information in the treatment of Schizophrenia (Lanktree et al., 2014). Mental health clinicians perceive that pharmacogenetic testing provides an explanation to patients regarding an increased sensitivity to medications (Dunbar et al., 2012). Thompson et al.

found 97.3% of psychiatrists and psychiatrist residents (n=113) perceived pharmacogenetic testing as being useful if a drug-drug interaction was indicated.

In addition, mental health clinicians found the test to be useful in developing a level of trust and rapport with patients (Dunbar et al., 2012). According to the clinicians, patients felt safer knowing that the clinician was aware of possible complications and side effects from medication. Clinicians predicted fewer side effects among medication and greater medication adherence among patients taking medications for psychiatric illness. Clinicians felt that this type of testing would be more beneficial for those classified as “abnormal metabolizers” who may be at a greater risk of side effects at low doses of medication (Dunbar, 2012).

Perceived professional impact. In a mixed methods study, psychiatrists and psychiatry residents believe that patients with mental illness would benefit from pharmacogenetic testing (mean = 3.03) (Hoop et al., 2010). Respondents used a scale of 1 (strongly disagree) to 4 (strongly agree) to determine responses to questions concerning the professional impact of pharmacogenetic testing. Psychiatrists and residents of psychiatry believe that pharmacogenetic testing would change the practice of psychiatry (mean = 2.77) and genetic testing would become the standard of care in the treatment of mental illness (n=113, 85.1%) (Hoop et al., 2010; Thompson et al., 2015). Additional psychiatrists (n=45) believe that genetics has a major influence on mental health (mean = 3.64, SD = 0.48) (Hoop et al., 2008). Similarly, in another quantitative study, among psychiatrists (n=57), clinician scientists (n=12), general practitioners (n=68), other specialties (n=4), and unknown specialties (n=27), there was no difference among specialties regarding the belief that pharmacogenetic testing will become the standard of

care ($p = 0.074$) (Walden et al., 2015). In addition, 80% of physicians believe that pharmacogenetic testing will become the standard of care in psychiatry (Walden et al., 2015). However, clinician scientists were more favorable ($p < .05$) regarding pharmacogenetic testing than psychiatrists (Walden et al., 2015).

Although 76.4% of respondents ($n=113$) who were engaged in pharmacogenetic testing were not familiar with genetic counseling, the majority of psychiatrists and psychiatry residents (72.6%) believe that genetic counseling would be helpful to discuss genetic results with patients (Thompson et al., 2015). In contrast, other researchers found that only 13% of psychiatrists ($n=45$) believe that genetic counselors are the most appropriate professional to provide genetic counseling to patients regarding the role of genetics in mental illness (Hoop et al., 2008). The majority of psychiatrists (78%) believe that the psychiatrist should be the person to provide genetic counseling to patients; however, 80% of psychiatrists had not ordered any genetic test within the last 5 years (Hoop et al., 2008). In another quantitative study, researchers found similar results where 83% of psychiatrists ($n=352$) believe that it is their role to discuss genetic information with patients and families (Finn et al., 2005). Approximately 23% of psychiatrists ($n=45$) believe that telling patients there is a genetic component to their illness will reduce anxiety about having a psychiatric disorder (Hoop et al., 2008).

Although the majority of psychiatrists believe that pharmacogenetics will become the standard of care, there is a consistent lack of knowledge among psychiatrists regarding such testing. In addition, clinicians who are early adopters or in academic or research settings have more training and knowledge of pharmacogenetic testing. Therefore, the previous study may not represent the average mental health clinician in

outpatient clinics. There are mixed results regarding whether genetic counseling should be conducted by psychiatrists or genetic counselors. Additional studies are needed to evaluate the competency of mental health clinicians regarding educating patients about pharmacogenetic testing results.

Perceived barriers. Although many benefits exist, mental health clinicians (n=33) identified several potential barriers to the CYP450 AmpliChip pharmacogenetic test in clinical practice (Dunbar et al., 2012). First of all, mental health clinicians were concerned that providers would focus more on the DNA blood test than using clinical judgement regarding the patient (Dunbar et al., 2012). In addition, other psychiatrists and residents of psychiatry (n=36) agreed (mean = 2.89, SD = 0.53) that providing secondary genetic information about susceptibility to a disease or prognosis is a possible risk (Hoop et al., 2010). Responses were on a scale from 1 (strongly disagree) to 4 (strongly agree). Other risks included a negative effect on patients' insurability (mean = 2.74, SD = 0.61) and causing patients psychological distress (mean = 2.85, SD = 0.58) (Hoop et al., 2010).

Several researchers found that mental health clinicians were concerned about the cost of the test (Dunbar et al., 2012; Hoop et al., 2010; Mrazek et al., 2007). In one study, clinicians were not provided with any information regarding the cost of the CYP450 AmpliChip pharmacogenetic test; however, the financial impact on patients was a concern and how it would impact clinical services to this vulnerable population (Dunbar et al., 2012). In another mixed methods study, researchers found that early adopter psychiatrists and residents (n=75) did not agree or disagree (mean =2.60) that pharmacogenetic testing would be too expensive for patients (Hoop et al., 2010). In another quantitative study, the majority of psychiatrists (69%) were not knowledgeable of

genetic laboratories in their local geographic area and 82% of respondents were not aware of insurance coverage for such testing (Hoop et al., 2008). However, early (48.7%) and future adopters (44.9%) were more likely to believe that insurance would cover pharmacogenetic testing compared to those who had not adopted testing in their practice (29.6%) (Stanek et al., 2011). Among psychiatrists (76.47%) and other mental health professionals (n=41) enrolled in a week-long course in psychiatric genomics, 59% of respondents were willing to pay \$375 for CYP2D6 and CYP2C19 genotyping by the end of the course and 95% of respondents were willing to participate in a research project to receive the test at no cost (Mrazek et al., 2007). According to Bousman and Hopwood (2016), uninsured patients can be charged up to \$3,800.00 with an optional payment plan for pharmacogenetic testing. However, some third-party payers may have agreements with the pharmacogenetic company to offer the test at a different cost (Bousman & Hopwood, 2016).

Another major concern among psychiatrists and psychiatric residents (n=66) regarding pharmacogenetic testing was perceived ethical concerns (Hoop et al., 2010). Respondents were given statements regarding ethically relevant aspects of such testing which were scaled from 1 (strongly disagree) to 4 (strongly agree). Respondents believed that psychiatrists must ensure confidentiality of results (mean = 3.35, SD = 0.54), demonstrate competence in interpretation of results (mean = 3.30, SD = 0.58), obtain an informed consent prior to testing (mean = 3.29, SD = 0.63), provide pretest and posttest counseling (mean = 3.20, SD = 0.66), provide tests only if benefits outweigh risks (mean = 3.05, SD = 0.51), and provide tests only to those who have decision making capacity (mean = 2.70, SD = 0.80) (Hoop et al., 2010).

In addition, clinicians were concerned about time restraints to order and perform the test in the clinical setting (Dunbar et al., 2012). For example, several respondents were concerned about practical issues such as having the test order forms readily available, delays in receiving test results, additional blood tests for patients, and unwarranted stress on the patient during this process leading to increased patient anxiety. Test results were received in eight days on average, however, some results were not available until forty-two days which became problematic for patients receiving treatment in an inpatient setting (Dunbar et al., 2012).

Despite perceived barriers, psychiatrists and psychiatry residents (n=17) in a mixed methods study are optimistic about pharmacogenetic testing and believe that such testing will not impact insurance or employment status more than the current diagnosis and treatment (Hoop et al., 2010). However, some believe that insurance and informed consent are the greatest barriers along with limited training on ethical issues. Although psychiatrists and psychiatry residents found pharmacogenetic testing useful for prescribing antidepressants and antipsychotics, respondents desire additional peer-reviewed published evidence to support pharmacogenetic testing. Some respondents believe that there is some general skepticism about the benefits of pharmacogenetic testing. Lastly, respondents were concerned that clinicians are using pharmacogenetic testing inappropriately and often presenting pharmacogenetics to patients as “the answer” rather than providing pretest and posttest counseling about the test and results (Hoop et al., 2010).

Overall, there are several authentic concerns about pharmacogenetic testing in psychiatry. The majority of mental health clinicians believe that pharmacogenetic testing

is useful but have some concerns regarding inappropriate use of the test, cost of the test, ethical concerns, potential impact on employment or insurance, and limited training on pharmacogenetic testing. Additional studies are needed to further assess these barriers in outpatient mental health clinics.

Implementation of Pharmacogenetic Testing in Mental Health

Pharmacogenetic testing is being used to guide treatment in a variety of illnesses including: cardiovascular disease, cancer, diabetes, autoimmune disease, infectious disease, pain management, and mental health (Hess et al., 2015). Presently, there are thirteen pharmacogenetic tests available in the United States in psychiatry (Bousman & Hopwood, 2016). Researchers have found pharmacogenetic testing to demonstrate clinical utility as a guide to medication selection in two open-label cohort studies and one randomized, double-blind controlled trial (Hall-Flavin et al., 2012; Hall-Flavin et al., 2013; Winner et al., 2013). In all three studies, participants who received pharmacogenetic testing experienced a greater improvement in depressive symptoms when compared to the unguided group (Hall-Flavin et al., 2012; Hall-Flavin et al., 2013; Winner, Carhart, Altar, Allen, & Dechairo, 2013). Future research is needed to determine when to implement pharmacogenetic testing, how to interpret results, and how to implement findings in clinical practice (e.g., medication planning and monitoring and patient and family education).

There is a lack of clear clinical guidelines on how to implement these tests into practice (Relling & Evans, 2015). In 2006, clinical guidelines for CYP2D6 and CYP2C19 were published for clinical dose recommendations for antipsychotics and antidepressants, selection of a laboratory, and interpretation of tests (de Leon, Armstrong,

& Cozza, 2006). In 2009, the Clinical Pharmacogenetics Implementation Consortium was formed to establish evidence-based guidelines for clinicians, but does not specify who should receive these tests (Relling & Klein, 2011). There is a need to understand how pharmacogenetic testing should be implemented in clinical decision-making and determine what type of patient would benefit the most from such testing (e.g., children/adolescent, adults, and geriatrics; patients with multiple medication failures; newly diagnosed patients; patients experiencing side effects from medications, etc.). According to Relling and Evans (2015), many predict each individual will have their entire genome sequenced early in life.

Two studies focused on the implementation of pharmacogenetic testing in psychiatry (Dunbar et al., 2012; Hoop et al., 2010). In a qualitative study, mental health clinicians (n=33) implemented the AmpliChip CYP 450 test to guide treatment of patients mostly with a diagnosis of a psychotic disorder or mood disorder (Dunbar et al., 2012). Clinicians completed a specific laboratory request form which was given to patients to take to a diagnostic clinic for a blood sample. The blood sample was sent to a central testing center and test results were posted electronically and paper copy sent to the clinicians. In this study, the laboratory was not familiar with the test resulting in extra blood samples taken from patients. In addition, there was a delay in clinicians receiving results. The average number of days from blood sample to dissemination was 8 days on average; however, some took 42 days to obtain results (Dunbar et al., 2012). A delay in results was a major barrier to clinicians ordering the test. In contrast, clinicians and scientists (n=168) who utilized another pharmacogenetic test, TaqMan Assays, obtained blood samples and received genotyping results within 48 hours (Walden et al., 2015).

In a mixed methods study, psychiatrists and psychiatry residents (n=75) discussed practices when ordering pharmacogenetic testing and receiving results (Hoop et al., 2010). The majority of psychiatrists and residents routinely informed patients of the test being ordered ($X^2 = 0.00$, $P = 1.000$), obtained patient's verbal consent ($X^2 = 0.22$, $P = 0.642$), informed patients about the cost of the test ($X^2 = 1.57$, $P = 0.211$), tested only patients with an immediate medical benefit ($X^2 = 0.061$, $P = 0.804$), and tested only those with a decisional capacity ($X^2 = 0.005$, $P = 0.942$). Standard practices among the majority of psychiatrists and residents included meeting with the patients to discuss results and answer questions ($X^2 = 0.43$, $P = 0.514$), filing results in patients' records ($X^2 = 4.68$, $P < .05$), and communicating results to primary care provider ($X^2 = 0.001$, $P = .979$). However, in another study, several clinicians did not find it necessary to order pharmacogenetic testing if a patient was not experiencing side effects from medications or if medication was stopped prior to results (Dunbar et al., 2012). In addition, clinicians reported they were unsure how to utilize the test results (Dunbar et al., 2012).

Overall, there is a consistent lack of guidance on how clinicians should use the information obtained from pharmacogenetic testing (Drozda, Muller, & Bishop, 2014). Other researchers have suggested implementing a multidisciplinary team to disseminate pharmacogenetic test results in a community health system (Dunnenburger et al., 2016). For example, the team would consist of a medical geneticist, a pharmacist, a nurse practitioner, and genetic counselors. The team would provide the following components: a billable service provider; documentation of family histories and medications; personnel to interpret test results discuss risks benefits, and limitations of testing; and a process for reporting results (Dunnenberger et al., 2016). Research suggests that the utilization of

pharmacogenetic testing in clinical practice will require structured algorithms and implementation of clinical decision support aids to guide medication prescribing (Overby et al., 2014; Relling & Evans, 2015). Relling and Evans (2015) propose that there is a growing body of evidence of pharmacogenetics expanding in the future and will become a significant component of evidence-based precision medicine.

Clinicians must know when to use pharmacogenetic testing, who should receive testing, and how to interpret results (Robertson, Brody, Buchanan, Kahn & McPherson, 2002). Currently, no guidelines exist for who should receive pharmacogenetic testing and how to translate results into practice (Abul-Husn, Owusu Obeng, Sanderson, Gottesman, & Scott, 2014). The implementation of pharmacogenetic testing will require collaboration between the clinician and laboratories which can be time consuming for busy clinicians (Burke, et al., 2016). Although these challenges exist, pharmacogenetic testing is a promising test that can assist clinicians in making informed clinical decision regarding medication planning and monitoring (Burke, et al., 2016; Davies, Conley, & Puskar, 2010).

Roger's Diffusion of Innovation Model

Rogers' Diffusion of Innovation (DOI) theory (Rogers, 2003) guides the study. DOI theory suggests innovation adoption involves five stages. In the *knowledge* stage (influenced by variables such as prior experience, perceived need for innovation, attitude toward change, personality variables, demographic variables, communication behavior, work environment, and others), an individual begins to seek information about the innovation to learn how and why it works. In the *persuasion* stage, an individual forms opinions and beliefs about the innovation is persuaded to accept it. In the *decision* stage,

an individual chooses to adopt or reject the innovation, followed by an *implementation* stage. The *confirmation* stage occurs after a decision has been made and the individual seeks support for his or her decision (Rogers, 2003).

This study will focus on the first four stages of innovation as described in DOI theory: knowledge of pharmacogenetic testing (*knowledge*), beliefs and opinions about pharmacogenetic testing (*persuasion*), factors that influence decisions to utilize pharmacogenetic testing (*decision*), and how the test is being implemented in current outpatient mental health clinics (*implementation*) (See Figure 1). Using DOI theory will illuminate the process of the adoption and diffusion of pharmacogenetic testing in mental health practice. This study will be used to identify elements of the theory that may influence adoption and diffusion rather than to explain why pharmacogenetics is being used in outpatient mental health clinics.

Although recent research describes the knowledge, perceptions, and opinions of psychiatrists and other healthcare professionals on pharmacogenetic testing, few studies explore knowledge and perceptions of those who are utilizing the test in clinical practice. The majority of mental health clinicians believe that pharmacogenetic testing will become the standard of care in psychiatry. However, throughout the literature there is a consistent lack of knowledge among healthcare providers regarding pharmacogenetic testing even though clinicians are ordering these tests. Despite the expansion of pharmacogenetic testing in psychiatry, there is a lack of clear guidelines for translating pharmacogenetic testing into clinical practice. In addition, no studies found examined the knowledge, perceptions and opinions of mental health advanced practice nurses and physician assistants who are utilizing pharmacogenetic testing in practice to guide

treatment decisions. Further research is needed to evaluate the knowledge level of pharmacogenetics among mental health clinicians and how these clinicians are implementing pharmacogenetics into clinical decision making and workflow.

Figure 1. Rogers' Diffusion of Innovation Theory

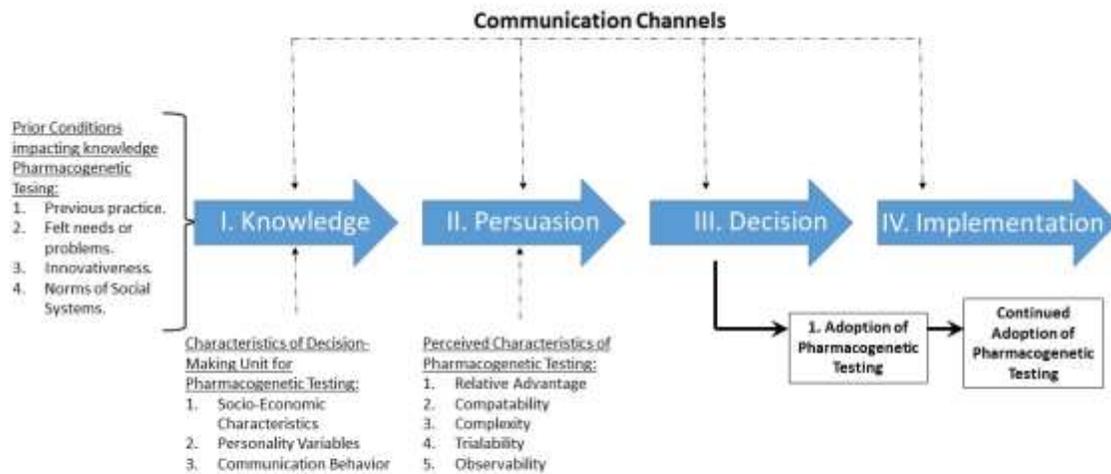


Figure 1. A Model of Five Stages of the Innovation-Decision Process (revised) by Rogers, E. (2003). *Diffusion of innovations* (5th ed.), Figure 5-1. Copyright 1995, 2003, 1962, 1971, 1983. New York, NY: The Free Press, A Division of Simon & Schuster, Inc. Reprinted with permission.

Chapter III

Design and Methods

Purpose

The purpose of this qualitative descriptive study is to evaluate mental health clinicians' perceived knowledge regarding pharmacogenetic testing, their attitude, receptivity towards, and confidence in pharmacogenetic testing, and how pharmacogenetic testing is being implemented to support precision medicine in outpatient clinics.

Specific Aims

1. To describe clinicians' perspectives on using pharmacogenetic testing in outpatient mental health clinics where such testing is routinely used, including their perceived knowledge, attitudes, and confidence in pharmacogenetic testing.
2. To describe clinicians' practices of using pharmacogenetic testing in outpatient mental health clinics including shared decision-making, determining who is tested, medication planning and monitoring, and patient and family education.

This study provides a solid foundation for future research to support precision medicine around pharmacogenetic testing and medications (e.g., examining patient perspectives and testing influence on outcomes such as decision conflict, medication adherence, and illness trajectories) and intervention development (e.g., patient decision aids) among patients with mental illness (Substance Abuse and Mental Health Services Administration, 2010).

Methodology

Research Design

Little is known about mental health clinicians' knowledge and perceptions of pharmacogenetic testing or how such testing is being implemented in outpatient mental health clinics. Therefore, we conducted a qualitative descriptive study with mental health clinicians, a research approach which is appropriate for exploratory, flexible, and holistic research questions (Mason, 2002; Polit & Beck, 2016).

Sample

Purposeful, maximum variation sampling included prescribing mental health clinicians in outpatient settings using pharmacogenetic testing in their current practice. Mental health clinicians including physicians, advanced practice nurses (i.e., clinical nurse specialists and nurse practitioners in psychiatry), and physician assistants who are actively utilizing pharmacogenetic testing and prescribing psychotropic medications in outpatient mental health clinics were eligible for inclusion in the study. Each clinician's perspective is necessary to understand how pharmacogenetic testing is being implemented in clinical practice. Exclusion criteria included clinicians who are not currently working in mental health outpatient clinics and are not utilizing pharmacogenetic testing in their current practice.

Sample Size and Configuration

The study will be conducted in mental health outpatient clinics located in upstate South Carolina, a region with approximately 80 mental health clinicians. Data collection will continue until data saturation is reached (Mason, 2002). The sample size was 28 participants. The P.I. interviewed approximately five to ten participants per month. In

order to reach data saturation recruitment was expanded to target mental health clinicians in other regions of South Carolina and nationally. In addition, a snowballing sampling technique was used by asking early informants to refer potential study participants.

The P.I. outreached to mental health clinics by flyer and telephone and email follow-ups, and used her network as a mental health provider. In addition, the P.I. utilized national organizations such as listservs to recruit potential participants. Interested participants contacted the P.I. by phone or email. Following a screening and verbal informed consent process, the P.I. scheduled a telephone or in-person interview with the participant per their preference. The interview was scheduled at a convenient and private time and place of the participant's choosing. Upon completion of the interview, the participant received a \$25 gift card for participation in the study.

Procedure

At the scheduled in-depth interview, the P.I. reconfirmed that all inclusion criteria were met and provided an opportunity to answer any questions that the participant may have regarding the study before the recording process begins. In addition, the P.I. discussed the participation of the study in detail and obtain both written and verbal consent before starting the in-depth interview. Following an informed consent process, the P.I. proceeded with an in-depth audio-recorded interview that lasted between 30 minutes and 60 minutes. Participants were re-contacted to clarify or confirm data, as determined during data analysis.

Instruments

Demographic form. Included variables important to clinician decision-making identified in literature review and according to DOI theory, e.g., age, gender, professional

title, years of experience as a mental health clinician, and years of experience using pharmacogenetic testing (see Appendix A) (Hoop et al., 2010; Walden et al., 2015).

Semi-structured interview guide. Included open-ended questions and follow-up probes, based on literature review and the P.I.'s clinical experience (see Appendix B). Participants were encouraged to speak freely, but a semi-structured interview ensured that certain topics are covered during the interview (Polit & Beck, 2016). Questions were framed around knowledge, persuasion, decision, and implementation stages of the DOI theory: e.g., knowledge, beliefs and opinions about pharmacogenetic testing, decision-making factors, and implementation strategies. The P.I. piloted the interview guide with two mental health clinicians and revised the interview guide with dissertation committee input. Additionally, questions were iteratively revised during data collection in response to developing themes and to saturate data categories.

Data Collection

Data collection was through semi-structured interviews conducted by the P.I. only. A semi-structured interview ensured that certain topics were covered during the interview (Polit & Beck, 2016). The P.I. encouraged the participant to talk freely about the topics on the interview guide. At the conclusion of the interview, the P.I. discussed with the participant that they may be contacted again if additional questions arise or if further clarification is needed once the P.I. has reflected on the information.

Data Management

In addition to audio recording the interview, the P.I. dictated notes immediately after the interview, to prevent information loss if there is an improper recording of the initial interview and ensure reliability of data (Polit & Beck, 2016). The interview and

notes were fully transcribed verbatim by a professional transcriptionist. Audio recordings were uploaded to a secure box drop on a secure computer. Transcripts were identified by a randomly assigned code to ensure participant privacy. The P.I. compared all transcripts to audio recordings to ensure accuracy. Transcripts were loaded into QSR NVivo 11, a qualitative data software package, for analysis. All hard copies, secure files, and written notes were stored in a secure, locked file cabinet and will be kept for seven years after the completion of the research project and manuscripts are published. Only the P.I. has access to the locked files.

Data Analysis

Data analysis and interpretation were based on qualitative descriptive analysis methods. A qualitative descriptive analysis approach was used to develop codes as outlined by Miles and Huberman (1994). Coding began as soon as the first interview has been transcribed and reviewed for accuracy. Each transcript was read and coded for clinicians' perspectives of pharmacogenetic testing (knowledge, attitudes, and confidence) and how it is being implemented in outpatient mental health clinics. After initial coding, the codes were grouped into categories. A constant comparison of the data was used with subsequent interviews to allow for an analysis of both within the individual case and across cases. Analysis prioritized identification of categories and themes related to the specific aims of the study.

Validity

The P.I. utilized several methods to ensure credibility and reliability of findings. Respondent validation was used to verify credibility of interpretations by confirming categories and themes with participants (Mason, 2002). The P.I. recorded field notes and

a summary of the interview after each interview to prevent loss of information if there is an improper recording of the initial interview (Polit & Beck, 2016). In addition, the P.I. kept records to justify steps of interpretation (Mason, 2002). Lastly, the P.I. worked closely with her advisor, an expert in qualitative descriptive research, who audited activities of the P.I. to enhance dependability and trustworthiness of the study.

Limitations

Limitations of the study included sampling and transferability. Sampling in qualitative research can be challenging since the access population may not represent the full target population and sample sizes may be significantly smaller (Polit & Beck, 2016). In this study, the P.I. recruited from the upstate region of South Carolina; however, since theory-saturation point was not achieved then the recruitment was expanded to other regions of South Carolina and the United States. Although the population does not represent a large geographic area, this study does have credibility (Polit & Beck, 2016) and represent clinicians who are utilizing pharmacogenetic testing in current outpatient mental health practices within this specified region. In addition, results are reported in terms of who responded (i.e., psychiatrist, advanced practice nurse, and physician assistants) to reduce sampling bias. This information is valuable to identify general patterns in clinicians' experiences with pharmacogenetic testing in outpatient mental health clinics.

Protection of Human Subjects

Approval was obtained for this study from the University of Missouri Health Sciences IRB. Purposeful, maximum variation sampling was used to recruit up to 28 participants who are prescribing mental health clinicians in outpatient mental health clinics. These clinicians have been using pharmacogenetic testing in their clinic.

Participants were not excluded based on age, gender, or race. Subjects did not include children, prisoners, or other vulnerable populations because the focus is on the experience of clinicians. There is the potential for pregnancy among participants; however, these women were not be excluded. Data collection techniques in this study were little or no risk to these subjects.

Inclusion criteria are: prescribing mental health clinicians (psychiatrists, physician assistants, advanced practice nurses (i.e., nurse practitioners and clinical nurse specialists), and clinical psychologists) who were working in outpatient clinics and are currently using pharmacogenetic testing in their clinical practice. The only exclusion criteria were mental health clinicians who were not prescribing medications and did not currently using pharmacogenetic testing in their practice.

Data collected from participants were recorded via digital audiotape during 30 to 60 minute in-depth interviews. Two audio recorders were used and one audio recording was deleted once it is verified that one audio is available. Observations of the participant including the physical setting and participant characteristics were documented immediately following the interview. Transcriptionists were provided with any required IRB training and the P.I. provided instructions to ensure anonymity, privacy, and confidentiality of participants and others that may be described by the participant. Within one week, the audio recordings were transcribed using Express Scribe Transcription Software and Microsoft Word software within the secure box drop. Transcripts were identified by a randomly assigned code to ensure privacy of the participant. The P.I. reviewed all transcripts by listening to the recording and reading along with the text to ensure accuracy. Transcripts were loaded into QSR NVivo 10, a qualitative data software

package, for analysis. All hard copies, secure files, and written notes by the P.I. were stored in a secure, locked file cabinet and will be kept seven years after completion of the research project and manuscripts are published. Only the P.I. has access to the locked files.

Risks. There are no physical, financial, legal or other risks to participants. Interviews focused on knowledge, perceptions, and implementation of pharmacogenetic testing and were not be emotionally upsetting to participants. The IRB at the University of Missouri reviewed and approved all study procedures. The P.I. explained the purpose of the study and obtain informed consent. Transcriptionists received any required IRB training. All data were de-identified and all study documents were locked in a secure file cabinet and kept seven years after completion of the research project and manuscripts are published.

Benefits. Benefits to participants were limited but participants have a better understanding of their use of pharmacogenetic testing through reflection during interviews. Benefits to mental health clinicians included a greater understanding of how pharmacogenetic testing is being utilized in mental health outpatient clinics, as well as any educational needs for clinicians who are using these tests. This in turn benefited clinicians to determine future clinical implications and integration of pharmacogenetic testing in routine clinical practice.

Participants may not personally benefit from interviews, but will contribute to better understanding of how pharmacogenetic testing is used in mental health outpatient clinics and clinicians' and patients' educational needs. Understanding how pharmacogenetic testing is being implemented can identify needed practice/policy

changes, improve patient outcomes, and provide a foundation for future intervention development.

Conclusion

Although many mental health clinicians believe that pharmacogenetic testing will become the standard of care, the previous literature consistently shows a lack of knowledge of pharmacogenetic testing. However, clinicians are ordering tests but are unable to translate results into clinical practice. No guidelines exist on how to implement pharmacogenetic testing in clinical decision making. Further studies are necessary to further evaluate the knowledge level of mental health clinicians utilizing pharmacogenetic testing and the development of evidence based guidelines for implementation of pharmacogenetic testing in clinical practice. The majority of studies have been conducted in academic or research settings rather than outpatient settings. This study provides a foundation for future studies to develop future education material and decision-making aids for mental health clinicians using pharmacogenetic testing in outpatient clinics.

Chapter IV

FINDINGS

Many mental health clinicians in this sample found pharmacogenetic testing to be helpful in their current practice. For many of these clinicians, the integration of Pharmacogenetic testing reduced trial and error in prescribing medications and improved patient outcomes. Clinicians in this sample found the test to be scientific and an additional tool for dosing medications. Additionally, clinicians found the test results to be consistent with patient reports regarding tolerability and efficacy of medications used in the past. This chapter focuses on the demographics of the sample, experiences of this sample of mental health clinicians as they use pharmacogenetic testing to guide their clinical decision making.

Demographics

Study participants included Nurse Practitioners (n=16), Nurse Practitioner/Clinical Nurse Specialist (n=3), Physician Assistants (n=2), and Medical Doctors Board Certified in Psychiatry (n=7) (Table 2). The majority of clinicians were females (n=20) and were between forty and sixty-nine years of age (n=24). Years of experience as a mental health clinician ranged from one year to thirty-five years. The majority of clinicians had one to five years of experience (n=21) using pharmacogenetic testing in clinical practice (Table 3). Most clinicians in this sample seen a range of 101 to 399 patients per month (n=21) and ordered pharmacogenetic testing for one to five percent of patients (n=15).

Table 2. Demographics

Professional Title	Age	Gender	Yrs. of Exp. Mental Health Clinician
NP/CNS (n=3)	20-29 (n=1)	Male	
NP (n=16)	30-39 (n=1)	(n=8)	
PA (n=2)	40-49 (n=8)	Female (n=20)	1-3 (n=6)
MD (n=7)	50-59 (n=8)		4-6 (n=5)
	60-69 (n=8)		7-10 (n=3)
	70-79 (n=2)		11-14 (n=1)
			15-18 (n=5)
			19-21 (n=2)
			22-25 (n=1)
			26-30 (n=2)
			31-35 (n=3)

*NP (Nurse Practitioner), CNS (Clinical Nurse Specialist), PA (Physician Assistant), MD (Medical Doctor)

Table 3. Description of Utilization of Pharmacogenetic Testing

Yrs./Months Using Pharmacogenetic Testing	Testing Company	Percentage of Patients Receiving Pharmacogenetic Testing (%)	Average Number of Patients Seen per Month
0-6 months (n=3)	GeneSight (n=26)		≤100 (n=4)
7-12 months (n=3)	Genomind (n=5)		101-199 (n=8)
1-2 years (n=11)	Millennium (n=2)	<1 (n=2)	200-299 (n=6)
3-5 years (n=10)	IDgenetix (n=1)	1-5 (n=15)	300-399 (n=7)
6-8 years (n=0)	Ventari (n=1)	6-10 (n=4)	400-499 (n=1)
9-12 years (n=1)	Natural	11-15 (n=0)	≥500 (n=2)
	Molecular (n=1)	16-20 (n=0)	
		21-29 (n=0)	
		30-39 (n=3)	
		40-49 (n=1)	
		50-59 (n=2)	
		>60 (n=1)	

A Tool for Prescribing

For many mental health clinicians in this sample, pharmacogenetic testing is an additional tool being utilized to assist with medication selection and dosing for patients with mental illness. One clinician stated, “I think it’s just given us another tool, another avenue, a little bit more information in choosing a medication.” Some clinicians believe that it is beneficial to utilize this tool with every patient while others found that it is not

feasible to do the test unless it is warranted medically. Clinicians perceive that this test provides them with more direction in prescribing medications. For example, the test guides the clinician to be more conservative or more aggressive with dosing. Some clinicians reported that usual practice is to “start low and go slow” with medications but the pharmacogenetic test helps to determine if you need to start even at a lower dose due to metabolism issues.

How the Test Works

The test is performed by conducting a buccal swab or saliva specimen to obtain a DNA sample. Most clinicians in this sample have the patient or nurse collect the sample. The clinician sends the DNA sample to the lab and results are sent to the clinician. The timeframe to receive results varied from 48 hours to three weeks.

The pharmacogenetic test provides information on how certain medications are metabolized including antipsychotics, antidepressants, anxiolytics, hypnotics, ADHD medications, mood stabilizers, pain medications and folic acid conversion. However, some of the tests also provided information beyond psychiatry. One clinician reported it is important for others to understand that “the test is not specific to psychiatry but specific to an individual’s DNA”. Clinicians agreed that the test looks at different genetic markers which may indicate if a patient will metabolize a medication more quickly or more slowly and may be more likely to have side effects from medication based on genetic markers DNA.

Choosing a Testing Company

Clinicians used a variety of pharmacogenetic tests in their practice including: Genesight, Genomind, Millennium, IDgenetix, Ventari, and Natural Molecular. The

majority of clinicians utilized Genesight or Genomind. Clinicians recommended doing research on the various pharmacogenetic testing companies before choosing a company. The majority of clinicians believed that it is important to choose a pharmacogenetic test with a good reputation and that is evidence based. Most clinician's recommended talking to other providers who are using pharmacogenetic testing in practice to learn about their experiences when choosing a testing company.

Initial Exposure to Pharmacogenetic Testing

The majority of clinicians in this sample learned about pharmacogenetic testing from peers that had been using the test in clinical practice. Additional clinicians learned about pharmacogenetic testing through educational settings including internships and curriculum in DNP, PhD, and Master's programs. Some read about pharmacogenetic testing in the literature but did not learn specifics about the test until the pharmacogenetic testing company representative came by their clinic. Many clinicians were exposed to pharmacogenetic testing through representative who came to the clinic or gave presentations at dinner meetings. Clinicians in this sample also learned about pharmacogenetic testing on their own through continuing education classes through online resources and conferences. In addition, one clinician reported that she learned about pharmacogenetic testing from social media by joining a private Facebook group for Psychiatric Nurse Practitioners.

Training Received on Pharmacogenetic Testing

Clinicians consistently reported that they did not receive formal training on how to use the pharmacogenetic testing in clinical practice. However, many clinicians reported that pharmacogenetic testing representatives provided information on obtaining

samples, billing, the usefulness of the test, and interpretation of the test. Clinicians reported that the pharmacogenetic company also provides access to geneticists and Pharm D's who are available to answer any questions regarding interpretation of the pharmacogenetic results. However, many clinicians stated that they have not utilized this resource. Most clinicians believe that the reports are easy to read and interpret the results. Many clinicians believe that they learned more from colleagues who had been using the test than from other sources. Some clinicians are learning on their own by seeking out educational conferences and courses on pharmacogenetic testing.

Factors Considered in Decision-Making

Clinicians in this sample discussed multiple factors that affected their decision to order pharmacogenetic testing on patients. Some clinicians felt that pharmacogenetic testing should be used for everyone, while others only ordered testing if they believed it was warranted. For example, if there was a medical reason or if there was a strong family history of mental illness. Additionally, some clinicians found the test to be beneficial among patient who were adopted and did not know their family history. Factors that affected decisions to order pharmacogenetic testing included cost of the test, benefits of the test, medication naïve versus medication failures, and severity of mental illness among patients.

Cost

The majority of clinicians in this sample considered the cost of the test a major factor in deciding to order the test. Several clinicians believed that it is not cost effective to order the test on everybody. One clinician stated, "I think it would be a great the thing to have on everybody. It would be irresponsible at this juncture to just randomly order it

on everybody.” Another clinician stated, “I generally don’t do it for anybody who doesn’t have insurance because it’s several thousand dollars”.

Clinicians found that government payers such as Medicare, Medicaid and Tricare covered the pharmacogenetic testing. However, private insurance payers did not cover the test. Clinicians reported that the pharmacogenetic testing companies provided a sliding scale for those who had private insurance. Most clinicians found the sliding scale to be reasonable and ranged from \$20 to \$330 depending on annual income. Clinicians found that most patients are unable to afford the test if they are paying cash for the test. Another clinician stated, “So it’s quite expensive still for commercial insurance. So, it has to be clinically relevant for that. But for Medicaid and Medicare population, I would do it all the time.” The majority of clinicians in this sample were less likely to order the test if patient is cash pay or has private insurance.

Benefits of Pharmacogenetic Testing

The benefits of pharmacogenetic testing was another major factor that influenced clinician’s decision to order pharmacogenetic testing. The majority of clinicians believe that the test is beneficial to both the provider and patient about 90 to 95% of the time. In this sample, clinicians found that treatment guided by pharmacogenetic testing was not only useful as a guide for prescribing medications but also lessened patient’s fears and anxieties about medication, validated patient’s experiences with previous medication trials, and improved tolerability and adherence of medications among patients with mental illness.

Lessen fears and anxieties. According to the clinicians in this sample, there are many benefits to using pharmacogenetic testing. One of the major benefits reported by

clinicians in this sample was that the utilization of pharmacogenetic testing may lessen patient's fears and anxieties from medications. A clinician stated that there was "a translation of folks from anxiety and fears about their own experiences with medications or what they have seen on the news, go to the point where they're actually able to get support with medicine that helps them." Similarly, another clinician stated, "So, the people who are a little leery of medication just to start with, that seemed to have helped a little bit for their anxieties about being on medicine at all any way."

Validates patient's experiences. Another benefit of pharmacogenetic testing according to clinicians is the test provides validation of a patient's previous experience with medications. One clinician stated, for patients with "problems with side effects or issues that they had, had a lot of times will be reinforced by this, that gives them a sense of validity for what the test results present." In turn, patients are more receptive to take medications. Another clinician stated, "I have had many patients who have felt more comfortable making the step in incorporating and using medications once we have the pharmacogenetic testing completed, because they know we are not just throwing something at them and hoping it sticks because it does for most people."

Improves tolerability and adherence of medications. Clinicians repeatedly reported that they found the utilization of pharmacogenetic testing improves efficacy and tolerability of medications among patients. One clinician stated, "Some of them may need a lower dose increased and if they metabolize too fast they might need high doses to achieve efficacy. And then some of them they have genetics, genes and they say they don't metabolize or have inhibitors of this or that, they can have more side effects. So, it helps with that to try and reduce side effects too as well based on the interpretation and

the testing is how it breaks it down.” Similarly, an additional clinician reported, “we may have made a better, more appropriate choice of medication and tolerability may be higher because of what our choices were.” Another clinician believed that pharmacogenetic guided treatment “improved medication adherence”. Overall, clinicians perceive that the pharmacogenetic test provides many benefits and is an additional resource or tool used to narrow down the options of medication choices when treating patients with mental illness.

Medication Naïve versus Multiple Medication Failures

Another deciding factor for clinicians in ordering pharmacogenetic testing was whether or not a patient was medication naïve or had multiple medication failures. There were several conflicting views among providers regarding this topic. The majority of clinicians in this sample agreed that patients who had experienced multiple failures of medication trials were excellent candidates for pharmacogenetic testing. However, some clinicians are considering pharmacogenetic testing earlier in treatment. One clinician stated, “I would say many times the test have shown that what I already knew to be true was that they aren’t going to respond to all these different medicines because they’ve already tried it, maybe I should start doing it earlier in the treatment which we have started to do. Thus far I kind of used it as the last resort because those are the people I thought of first to try it on. Because they are having such a hard time finding medication that would work, but now I’m starting to do it on the ones a little bit earlier.”

Medication naïve. Approximately 18% of clinicians in the sample believed that everybody should be tested and would benefit from the results including patients who have never tried medications. One clinician stated, “I haven’t had, never seen anybody

that I thought didn't benefit, somewhat from having the testing. Even if all it does is show that you're on the right medicine at least we know that."

Additionally, providers who are seeing adolescents and children were more favorable to ordering pharmacogenetic testing earlier in treatment. One clinician stated, "And that's pretty much my rule with someone that's that young and never been on medications never really had major issues that they really having some significant depression. I just don't think that it's something we need to even wait on." Similarly, another clinician reported, "I utilize in situations where -- even in the medication naïve patients, patient who has never been on medications. If parents were exceedingly cautious, exceedingly anxious about -- I think they are on this medication for the first time and I don't want my kid to be a Guinea pig, I've heard that a lot through the years."

Multiple medication failures. Most clinicians in this sample, considered pharmacogenetic testing for patients who had multiple failures of medications. One clinician reported, "I would not order this if they had a response to either the first -- one of the two or three medicines I tried -- a certain logical sequence. So, if they had a response, I'd probably not get the testing." The same clinician reported that he has "only been using it for patients who use at least two antidepressants or two mood stabilizers or two antipsychotics at therapeutic doses." Similarly, another clinician stated, "Usually I order for patients who have failed at least -- usually three different medications for the same diagnosis or the same set of symptoms". While another clinician agreed, "I generally save it for ones that have failed three or four trials of medicine."

Another clinician reported, "Well, so often patients show who have finally got to see me and have probably been on the same medication by the time they get to me. And

they're either really frustrated and it's almost like this still isn't working and... or it's not working the way that it used to work and I'm not quite sure where we need to go so, and that's a good sign too. So, I say, "Okay, instead of just going on a wild goose chase trying to figure out where we go next, you know why don't we be a little more scientific about it now and go ahead and do the pharmacogenetic testing?"

Clinicians consistently agreed that they are more likely to order pharmacogenetic testing when patient's report that they have been on medications for years with limited response. One clinician stated, "I mean again like I find the most effective population to be the people who have repeatedly failed different medication trials. I mean and the reasons for that can obviously be complex, but I think in those patients it helps to give them a renewed confidence in the treatment process. Sometimes people come to me, you know I've been depressed for 20 years, I've taken like 15 medications and nothing ever helps. I think nothing is ever going to help. So, I've found that to be like a really great tool for those kinds of patients."

Multiple Adverse Effects

A substantial deciding factor for ordering pharmacogenetic testing was if the patient experienced multiple adverse effects from medications. One clinician stated, "primarily I've been using it for people who have tried a couple of different medicines and they didn't work or they have had side effects and couldn't tolerate anything and you know get testing, at that point and see if we can optimize their treatment." Similarly, another clinician reported, "There is several things that tell me that I probably need to look at genetic testing. First would be had they had some strange reactions to medications either medicines don't work for them or they get very sensitivity reactions they get

maybe get side effects or average effects that would normally be seeing as the dose was too high for example.” Clinicians in this sample found that the pharmacogenetic testing report was beneficial in understanding why patients were having adverse effects. Clinicians in the sample concur that adverse effects are a major deciding factor in ordering pharmacogenetic testing.

Severity of Mental Illness

Another deciding factor in ordering pharmacogenetic testing among clinicians is the severity of the mental illness. Clinicians were more likely to order pharmacogenetic testing for patients who had multiple hospitalizations, chronic serious mental illness, or required higher doses of medications with limited response. One clinician reported that they are more likely to order pharmacogenetic testing depending on the severity of symptoms, for example if the patient “couldn’t get out of bed or couldn’t function.” Another clinician reported, “If somebody has had significant adverse reaction certain kinds of medicine or if they express frustration with medicine, if they express that, they feel like they're being treated like a guinea pig it tends to – even them out a lot more.” In addition, clinicians were more likely to order testing if patients required multiple hospitalizations for their mental illness.

The majority of the clinicians agreed that they would not order pharmacogenetic testing if a patient was responding well to their medication without any significant adverse effects of the medication. Most clinicians believed that pharmacogenetic testing should be used only if medically warranted and not for everyone. One clinician stated, “It’s not very often that I recommend it for someone brand new unless they specifically request it because I don’t think the testing should be a substitute to clinical judgement

also. And what I certainly try to point out to my patients is that the testing it's not being used for diagnostic purposes and that's why with the new patient that at first you got to try to get a sense of what your working diagnosis or diagnosis might be. So, if that's the case, then I'm not necessarily rushing to get the genomic testing done, I want to see if we are on the right track based on what the assumed diagnosis might be before we all start thinking about that."

Perceptions of Clinicians

Overall, clinicians in this sample perceived pharmacogenetic testing to be a valuable tool in their clinical practice. One clinician stated that pharmacogenetic testing allows "prescribers to make more educated decisions and more educated recommendations." Another clinician stated, "I'm using it more and more as I become more comfortable with it and have seen more success with it that I do it a lot." This section will discuss the impact of pharmacogenetic testing on clinical decision-making, how clinicians perceive shared-decision making in conjunction with pharmacogenetic testing, and populations who do not benefit from pharmacogenetic testing.

Impact on Clinical Decision-Making

Clinicians have conflicting views on the impact of pharmacogenetic testing on clinical decision making. Most clinicians found that pharmacogenetic testing can positive influence clinical decision-making by providing reassurance to the clinician and patient, explain why patients have been resistant to treatment, reduce trial and error, and give permission to go beyond normal prescribing practices. However, some clinicians in the sample reported that pharmacogenetic testing could negatively impact clinical decision-making in certain situations.

Reassuring to Clinician and Patient

Most clinicians found pharmacogenetic testing to be a significant piece in clinical decision making. First of all, clinicians believe that the testing is reassuring. One clinician states that the test is “reassuring that what we’re doing is on the right track and then we just need to tweak the dose up or down sometimes”. In addition, patients were also reassured by the results. Another clinician stated, “it sometimes just kind of helps to clarify like why patients haven’t done well which is also reassuring for them like I had a patient recently who you know had not – had good affect with a whole variety of medications. And when we got their testing back, all of them were on the – do not – for lack of a better term do not use list. Then they – so then they felt oh, it wasn’t in my head. Like there actually seems to be indication that these weren’t very good medications for me in particular to take.”

Resistant to Treatment

Many clinicians found that pharmacogenetic testing was helpful to explain why patients were resistant to treatment. One clinician explained, “it’s sometime interesting to see patients that have been on five or six SSRI’s, which I mean should be kind of questioned to begin with anyway, but then you know that they get this list of basically all SSRI’s in the red column so to speak. And I see that this is why that sometimes patients are more resistant to treatment and can make, it can explain why, sometimes we get this niche and the patients are difficult and then we get results back that confirmed that they just don’t metabolize medications in a way that we would expect.” Similarly, another clinician found that “there has been a couple of cases where the child did have kind of a lot of metabolic issues and it did sort of explain why they hadn’t done well on past

medicines.” Clinicians have found test results to be consistent with clinical findings. One clinician stated, “I thought it’s really helpful and I have seen it a lot of correlation between medication that they have told me in the past that this didn’t work or it would make them miserable and you know that’s pretty consistent, not always, but you know I have learned that I can rely on those, and also I think they have a better success rate with the medication.”

Guessing Game

Clinicians in this sample believe that pharmacogenetic testing has positively impacted their clinical decision making. One clinician stated, “Yeah I wouldn’t keep doing it if I didn’t see it was beneficial. So, clearly I’ve seen results with my patients.” Several clinicians reported that pharmacogenetic testing reduces trial and error and takes away the “guesswork”. One clinician described it as the following: “And what will usually happen is doctors use medications that they think are safe, appropriate to the diagnosis if they had success with other patients, but everyone is different. So, what works for one patient may not work for another. So, usually it’s just kind of a guessing game. You’re picking something out of a hat. You keep picking out of the hat until you find something that’s good enough. And then you generally stop looking, but is that the optimal medication for the patient, you know is there something else. If you would have tried three more things, would you have found something that worked even better. I mean, who knows unless you’re going to do that, but who wants to put a patient on 35 medicines and then pick the best one.” Another clinician stated, “I think it’s beneficial for the patient if for no other reason than it often times makes them feel like we know what we’re doing and we’re not just guessing.” An additional clinician reported, “It makes

their chance of showing – of no showing to future appointments a lot less because it gives people more hope that we're not taking a guess at what types of medicine, we have an educated guess." Overall, clinicians believe that pharmacogenetic testing provides them with an "educated guess" rather than the traditional trial and error approach and may reduce the timeframe to achieve stability with medication.

Going Beyond Usual Prescribing Practices

Several clinicians reported how pharmacogenetic testing impacted their clinical decision making by giving them permission to go beyond their normal choice of treatment. For example, one clinician stated, "Also because – specifically because of the serotonin transporter marker. It sort of forces me to consider non-SSRI medications and in young people more than I probably would if I did not have the genetic testing available, because typically you know SSRI's you know more well studied in young people or in many – not all that do have FDA indications in minors. And you know, so just classically you know have always – not always but majority of the time you know use SSRIs first line for both anxiety and depression and anyone under the age of 18 as opposed to an SNRI Wellbutrin or something. And so having done this testing has sort of opened my eyes to how many people are likely be co-responders to SSRIs because of the serotonin transporter and so I'm sort of considering non-SSRI medicines probably early in the course of – earlier in the course of treatment now than I would. But certainly, has been beneficial to me in terms of you know helping steer my prescribing practices in a direction that I think is more beneficial to my patients."

Another clinician stated, "And so sometime you know thinking outside the box being what I consider relative new to practice there are some meds that I just don't go to

because I'm not as familiar with them. They are not as readily used and it's kind of forced me to learn more meds and step outside of my comfort zone a little bit when I'm prescribing because they are indicated as being somewhat helpful to the patient and they are things that haven't been tried before. And so that to me has been a little helpful because I don't necessarily think about some of those medications...so that has helped – that has helped me and forced me to kind of move outside of the standard you know, you know the SSRI's, the SNRI's for depression and that type of thing you know.” Additional clinicians found that they were more likely to increase doses of medication if the patient was found to be a fast metabolizer of medication, whereas, they would normally be more cautious about doing so.

Not Always Helpful

Approximately 25% of clinicians were unsure if changes guided by the pharmacogenetic test made a significant difference in clinical decision making. For example, one clinician who had been using pharmacogenetic testing for about six months stated, “I'm not sure the changes that we make have made that much different. I had one lady that – a couple of other things she was on was fine. And then we made another – I think we got her off Seroquel and put her on Remeron or something like that or Trazodone or something. And it didn't work as well. But she felt better about it because she would gain so much weight on Seroquel anyway. She wasn't really sleeping that great on it. But I think she was sleeping better on Seroquel than when we made the change. So I get a little confused sometimes – I'm not sure that it's great as what I thought it was going to do when we first started. But I think the jury is still out. I haven't been doing it long enough really with enough people to see.” The same clinician has

found it to be beneficial in some cases, he states “But it’s helped me guide me in a couple of cases. I’m being more open to it.”

Another clinician found that the results were not as helpful in clinical decision-making when the results revealed tolerability of most medications. For example, one clinician found that in adolescents and children, “the majority of the time that kind of, the report might show that tolerate every medicine fine, as far as being able to metabolize it and maybe they just haven’t done well on medicine because they had just side effect for what not.” In contrast, a clinician who has been using pharmacogenetic testing in practice for one year stated “I have found helpful most of the time that probably about 75% they say this and this didn’t work and had bad side effects. The testing does correlate with that pretty good. It's spot-on with it.” Another clinician perceived that the test was accurate 50% of the time. This clinician reported that the test has “helped in a couple of cases, but it’s not been life changing.”

Some clinicians found that the medications that were suggested may not be clinically indicated for the symptoms or illness that the patient is experiencing. For example, one clinician stated, “even in the green column the medicine might not help their symptoms.” Another clinician reported, “Just because the medicines that they suggest like on the Genesight panel, on the psychotropic panel for example will show all of the antipsychotics, all of the anxiety medicines, all the antidepressants and typically, I’d say about 10% of the time, it’s – like most of the time it’s very bad side effects to a medicine. It will show up as a potential medicine that they should avoid. The other 90% of that medicine may be listed of like a green or caution. So clinically it’s sometimes frustrating and it doesn’t you know it’s not an exact science and I understand that and all.

Sometimes it's frustrating because the data doesn't support the way that the patient is reporting the way the medicine makes them feel." Another clinician stated, "I am willing to recommend for patients who I feel would benefit from it. But I don't know. Based on my experience, I don't want patients to have their hopes high and then get frustrated."

An additional clinician found the test to be less helpful in patients who already know what works for them. This clinician stated, "It's been some rare occasions when it wasn't helpful and I don't feel it's just been based off the test. I think it's just been off the sense of importance of what the patient has been saying and what they think works for them and what they don't feel like works for them, like I've when patients say okay, I don't care what GeneSight testing? This is what I know works for me, so." Although, these clinicians continue to utilize pharmacogenetic testing to guide their treatment, there are still some uncertainties about the impact on clinical decision making and outcomes.

Despite concerns about the impact on clinical decision making, many clinicians believe that the test is beneficial for many patients in their clinical practice. One client stated, "I wish I could just do it for everyone, because my motto is do no harm." I'm not into you know needle assessing and if where practicing the medications and we're not really sure how the body is receiving that medication, that to me seems inefficient and, and it's just not the best practice. So, I know it's just a you know a probability thing. I know it's not a you know an absolute scientific way to know what method would work, but at least to eliminates a lot of the ones that aren't going to work." The majority of clinicians believe that the test provides insight on how to approach patients and avoid wasted time and unwarranted suffering for patients. One clinician reported, "It's worked for me, it works that's why I keep using it."

Shared Decision-Making

Clinicians views on shared decision-making varied within the sample. The majority of clinicians utilized shared decision-making in their clinical practice and found the pharmacogenetic test to be a tool useful in the implementation of shared decision-making. However, many clinicians reported that they would implement shared decision-making with or without the test. Most clinicians viewed shared decision-making as a team effort and implemented shared decision-making through open dialogue, giving the patient treatment options, and clinical judgement.

Open Dialogue

Clinicians believed that it was important to discuss side effects of medications, listen to the patient's concerns, review previous medications, and explain clinicians' recommendations. Most clinicians engaged in open dialogue with the patient to discuss treatment options guided by pharmacogenetic testing to develop a mutually agreed upon treatment plan. One clinician described the process as the following, "What I usually do when I show it to them is that I try to explain that the differences of the medicines that state that they are that are listed and it might possibly work and I try to give them some information, accurate information about those medicines and then help and then they can help me figure out which ones that they want to try first." Similarly, another clinician stated they implemented shared decision-making "by having a dialogue with the screen up and asking open-ended questions like what do you think we can try this and what do you feel. So, I use a lot of those kinds of questions from the beginning. I also at times will show them the documentation and tell them what I'm going to document. And if

that's okay with them, do they feel that that am I getting it, just right? I use that word a lot, does that sound, right? So that's how I use shared decision-making.”

Another clinician discussed how shared decision-making helps to build rapport with the patient. This clinician stated, “Absolutely because – yeah, because we're both really excited to get the results and I like take a look at it and we kind of bond about oh well no wonder that didn't work or no wonder you couldn't tolerate that – there it is right there, you know. So, I think it really does facilitate that relationship even more.” In addition, shared decision-making allows patients to feel comfortable asking questions. One clinician stated, “And they know I'm always open to them asking me questions.”

Giving Patient Options

The majority of clinicians believed that it was important to give the patient options in treatment. One clinician stated, “I think 90 percent of the patients like that and I think a few are looking for someone just to tell them what to do.” Another clinician stated, “Yeah, we look at the test results and say okay what do you think – I'm very collaborative with my patients and say do you think this means something. Do you want to try a little higher dose you know most of the time the higher doses mean – more side effects and I'm like do you want to try a higher so you metabolize it fast or do you want to try something different.”

In addition, clinicians want the patient to be comfortable with the treatment decision. One clinician stated, “It's a big thing, it's a big thing because I will make the comment at times I'm like probably several times you know we will come, you know we'll get together with this test and decide what you know I offer you my recommendation and you see how you feel about that because you are the one going to be

taking the medication and you need to be comfortable with the decision, that we have come to.” Another clinician stated, “You know actually – that’s my whole model is very collaborative and with my patient and their families, sometimes their family likes to come to and participate and helping the patient make a decision.”

Similarly, another clinician stated, “I mean I always tell my patients from day one that I see treatments as shared process period, because if they’re not happy or comfortable with their treatment then obviously I feel like we’re not having an effective therapeutic alliance. So, I don’t know that it really enhances it that much. For me other than the fact that you know I just try to present it as one more tool that I’m bringing them so that we can make the best possible decisions for their treatments together.” Overall, most clinicians believe that although the clinician is the one who provides the patient with the treatment recommendation, but the patient decides if they want to take the medication or not.

Clinical Judgement

In addition to giving the patient treatment options, many clinicians agreed that the final treatment decision-making should be based on the clinician’s judgement and expertise. One clinician stated, “I think it is important that the final decision-making has come down to the prescribers’ judgment.” Although many clinicians in the sample agreed that the final treatment decision is based on the clinician’s clinical judgment, the clinicians emphasized the importance of explaining their rationale to the patient.

For example, one clinician stated, “I basically, review the results and make my own decisions about what the direction would be -- I mean I explain those – explain when I’m changing medicines, why I’m doing it. So, part if that discussion is well -- it looks

like you didn't respond to any of these medications in this class. Maybe we just haven't found the right one yet. Or the reason that we switch to another class -- I try to explain that. But that I would do that with genetic testing or not." Similarly, another clinician stated, "I'm a pretty easy-going guy. I don't, obviously prescribe whatever the patients want but I am very transparent with them. And I educate them fully before I make any medicine prescription and I tell them all the side effects. I'll explain the neurotransmitters I explain why the medicine is working of them. I'll explain them what their diagnoses are and I think -- generally the patients respond to me pretty well because I'm very open with them, and straightforward and the genetic testing is no difference there." An additional clinician stated, "you know they need to be included, they need to be feel like they are empowered in that because it is them it's, it's, it's wrong to welcome to testing for them and we're going over it, before I explain the test in office. I say, "now are you feeling comfortable? You see what the medications we are looking at here." And I will tell them the rationale of why I'm looking at maybe two or three particular medications."

Populations Who Do Not Benefit from Pharmacogenetic Testing

While most clinicians believed that pharmacogenetic testing was not contraindicated for anyone, clinicians were able to identify persons that may not benefit from such testing. One clinician stated, "I haven't had anyone that I would say I didn't think would benefit from it. But I haven't, like I don't use it on everyone who walks through the door either." However, several clinicians agreed that patients who were stable on current medications, medication naïve, preferred alternative treatment, or persons with cognitive distortions or personality disorders were not ideal candidates for pharmacogenetic testing.

Stable on Medications

Many clinicians believed that patients with a straightforward diagnosis or stable on their current medications would not benefit from testing. One clinician stated, “I think that that’s a kind of jumping ahead of it and depending on the expense might not be worth it. I wouldn’t do it on someone that was doing well on medication and were stable and there was no need to change.” Another clinician stated, “Typically I’m not going to do genetic testing on the person that comes in and I make a diagnosis and send out a treatment plan and they respond to that treatment plan. I’m not going to do genetic testing on them.” Most clinicians believed that if the patient is doing well with the current treatment plan then it would unnecessary to perform pharmacogenetic testing.

Medication Naive

In addition, many clinicians believed that patients who were classified as medication naïve would not benefit from testing. One clinician stated, “Well, again if you have somebody coming in and you know, they’re straightforward, maybe their medication naïve, this is the first time having any, any, you know first time seeing any provider for depression say or anxiety. You know, I’m not going to rush right out. I don’t think those people, would they benefit? I think they would, but it doesn’t make sense at this point in time to spend their money nor are they likely to spend the money to do the testing if they haven’t had any complications.”

Another clinician with similar views stated, “I don’t necessarily give it to people who are treatment naïve and just walk in through the door. I know the genetic companies tell us that will improve their treatment but you know lots of times, you know whatever we give them doesn’t necessarily change our treatment that much. Let’s say you know

there is a kid with ADHD who comes in and you have to pick which stimulant to use they are pretty much metabolized the same way and they come out in the same column on the genetic testing and they wouldn't have it's not in a genetic test and tells us that they're more likely to cause a side effect. The first-line treatments that their Medicaid plan covers, we still have to start with trying them. You know, there's no point giving testing to everybody who walks through the door considering all the side effects, I think."

An additional clinician stated, "So, a lot of them are naïve to medicine when they've come and my chances of picking something that works is pretty good." Another clinician stated, "And so the first time, you know they are a virgin to any SSRI's and their depressed, I'm not going to do that. I'm going to use my clinical knowledge and symptoms and start them on an SSRI. Or same thing starting Lamictal on someone who is cyclothymic, Bipolar Type 2. Yeah, no every patient does not need this." Clinicians consistently reported that they would save the test for persons with previous medication trials and failures.

Alternative Treatment

Several clinicians reported that it would not be feasible to order pharmacogenetic testing on patients who were seeking non-pharmacological treatment. For example, one clinician stated that she would not order pharmacogenetic testing for "people who don't do well with pharmaco, pharmaco, pharmaceuticals you know who prefer natural things. And for them I would, and that's a lot of my practice actually, for those people I would not even think about the gene testing, I would think of you know out of the box, or think about innovative care. And I'd think about complementary alternative which I do anyway, I mean I do that with everyone. So, what I would do is try to refer them to

somebody who specializes in, in that area. You know in homeopath, either homeopathy or osteopathy, or somebody acupuncture, somebody that does more natural medicine.”

Another clinician stated, “well I mean obviously if I got a patient that comes in and they we decide that psychotherapy is the route we are going right now, I don’t mention the test. I don’t even initiate the conversation about the test because they are one made it very clear that they are opposed to medication or that really isn’t that much of an indication for medication.”

Cognitive Distortions or Personality Disorders

Several clinicians reported that they would not order pharmacogenetic testing on patients with disorders that may limit their understanding of the test. One clinician stated, “I would have to say the only patient that I would probably be hesitant in doing the testing would be one that really doesn’t have a grasp of what the testing is going to actually provide and how it translates into treatment.”

Another clinician stated that they would not order pharmacogenetic testing in someone with a personality disorder. This clinician reported, “Some personality disorders like, there wasn’t really a well-established mood disorder where medications in general wouldn’t be recommending or there are patients that probably might get false hope behind the results of a genetic testing. But most of the patients I see have a mental disorder, so I guess there are patients using that had only personality disorders maybe.”

Lastly, some clinicians in this sample believed that patients with significant cognitive distortions and paranoia would not benefit from pharmacogenetic testing. One clinician stated that the patients are “paranoid about it, you know, what are you, are you practicing this on me trying to get something? You know, I think it's again just paranoid

of what is it going to say? It may be revealing something that I don't want to know. That kind of thinking.” Clinicians found that patients with paranoia or cognitive distortion were more likely to refuse the test.

Risk and Downsides

Pharmacogenetic testing may pose risks to the patient. Clinicians in this sample were able to identify several risks and downsides to pharmacogenetic guided treatment. Some major concerns among clinicians included lack of evidence, simplicity versus too scientific, medication barriers, cost of the test, and misinterpretation or misuse of the data. However, some clinicians believe that there are minimal or no risks to using pharmacogenetic testing in clinical practice.

Lack of Evidence

Some clinicians believed that the evidence is still lacking regarding pharmacogenetic testing. Several clinicians found that the test is not 100% fool proof and there is still room for improvement. Clinicians found that the test can place them in an awkward position when the results are not consistent with the patient’s report and therefore, place doubt in the patient. One clinician stated, “Sometimes if you have a patient that has been successful on medication and then the results come back and it falls into the red category or whether it appears the medication should not be beneficial. I think it could potentially create doubt in the patients or can put the provider in a place where decision to continue a medication or stop the medication.” Similarly, another clinician stated, “But there have been times when I kept patients on medications that at least from the testing appear should not be effective. And the fact that I have had patients that, you know, for example, one lady’s testing came back and you know the one’s in the

red column were the only medicines that every worked for her it did cause some weight but it was the only that ever worked for her and I would have never tried her on it if I knew it was in the red column probably. So, it's not like 100% fool proof, I think."

Another clinician discussed her concern about the lack of evidence in psychiatry for pharmacogenetic testing in patients with Schizophrenia and Bipolar Disorder. This clinician stated, "So, I have pretty sick patients, a lot of bipolar, schizophrenia and I think that the evidence for that population, it isn't quite there yet. Certainly, if you're going to go on evidence based right now, in psychiatry the evidence base is there for depression. I think other illnesses, it's coming along, but the duplication studies aren't quite there yet. The strength of the evidence isn't quite there yet which doesn't mean that it doesn't work, it just means the research hasn't been enough to say definitively yet there is definitely a difference if you action this gene variations. You know I work in community health , and that's something that was important to me, because I do think the test has value and I think for the more vulnerable populations that have the highest burden of medical illnesses and disease burden and higher rate of homelessness and substance abuse that any type of kind of cutting edge technology which I think is how genomics is viewed right now that that is the population that should absolutely have access to this type of testing, but that's not ethics solution of others. I think it has value for a lot of different people, but I don't think the evidence – the research is not there yet today to suggest tests to everyone that walks through your door."

Some clinicians are concerned about the efficacy of the test since there is lacking evidence and research on pharmacogenetic testing among different patient populations the evidence is not clinically applicable to some patients. Another clinician stated, "you

know if you look at some of the literature it says you know it's not a 100% fool proof and if you use – I guess if you take it only at face value and only we'll prescribe what's in the green column and only if FDA indicated this dose or whatever. I think if you rely only on that and fail to exercise any type of clinical judgment that could be a downside to it.”

Clinicians emphasize the importance of using clinical judgment along with the tool but realizing that the test is not 100% fool proof at this point.

Simplicity versus Scientific

Some clinicians view the test as too simplistic while others view the test as too scientific. The reports from the different pharmacogenetic testing companies vary. The majority of clinicians in this sample used Genesight or Genomind for pharmacogenetic testing. Several clinicians reported that the Genesight test report is displayed using a “green, yellow, and red” column for medications and they like the simplicity of the report. One clinician stated, “I really like the GeneSight for now because they are kind of, you know genetics for dummies. (*laughing*) They have a green light status meaning that all the particular drugs in that category are metabolized normally. And then they have a yellow kind caution which you know, some of the medications that the patient might have trouble with, they are ultra-rapid metabolizers or ultra-slow metabolizers. And they have lots of side effects and things like that or the drug might not be effective and then there's a red category for you know, more significant gene-gene interactions or I mean drug-gene interactions or drug-drug interactions. So, I try to avoid them.” However, another clinician using Genesight testing stated, “They do put footnotes to describe clinical considerations and the verbiages that's used for describing what they have actually tested, but I think it is a little bit too scientific.”

In contrast, other clinicians preferred a more detailed explanation and summary of the genes rather than the “green, yellow, and red” list of medications. One clinician stated, “Well I was originally trained on the Genomind profile and I like it that it is a summary of the genes and the results of the genes in the first two pages and I like to know what is the gene and what was the results because that helps me make decisions better. Rather than like with GeneSight you have to flip through the pages and then try and put together yourself as far as a look of all the variants or all the polymorphisms. So, I don’t like having to do that it causes me extra work and extra paper work. And I also don’t care for the red yellow green report because when you are working with genes you are not working with like a vitamin D level that there is a good or a bad. It’s when you look at DNA it will only tell you what the body is capable of making. It won’t tell you what the body actually make or if that gene is expressed. So that’s where the clinical judgment is to come in a clinical training and so I don’t care for the GeneSight or the Millennium reports because they, try to make the results, I don’t know genetics for dummies and I think it does the patient a disservice to do that. It’s more scientific it isn’t meant to be look at the green column and that’s what you can prescribe for a patient because that’s not necessarily true.”

Clinicians have conflicting views on pharmacogenetic testing reports. Some clinicians prefer to look at the “green, red, and yellow” columns for list of medications, whereas, other clinicians prefer to look at the DNA and the science behind potential gene-drug interactions. However, all clinicians believed that clinical judgement should not be replaced by pharmacogenetic testing, but rather as a supplemental tool in decision-making.

Medication Barriers

Several conflicts were identified with medications including the cost of medications and the off-label use of medications. The cost of medications was a major barrier and impacted many clinician's decision to order pharmacogenetic testing for their patients. One clinician stated, "And one of the other thing that's so important is we have to always keep in mind is how much will these meds cost these patients to make a switch. Because for example the only medication to show up would be desirable to brings users direct category, if those are medications that are not available in generic form and a patient is a self-paid patient, for example, and they have no insurance, anything like that then you might just be cost prohibitive for them to consider certain medications. So, I always have to keep that in mind too. So, I run into problems when, you know, the testing might show that they need a certain group of medicines and the insurance might not necessarily cover it and there's an argument in favor of getting a prior authorization approved but sometimes it works and sometimes it doesn't."

Clinicians found that insurance may not cover the newer medications or off-label uses of medications even if these medications are indicated by the pharmacogenetic test findings. One clinician stated, "Sometimes it's just the cost factor the newer medicine and we get some samples but that doesn't really help because the samples are gone and then they have to go back to making their decision about paying for them if we make a change." Similarly, another clinician stated, "To be honest the Medicaid will not pay for off labeled medicines. So, a lot of time the reports have all of these newer medicines that are out now, the Trintellix, and the Viibryd, and Pristiq. And all these things, but Medicaid will not pay for a child to take those because they're off label. So, I cannot

even consider them even though if I were in private practice or a private insurance. I might even consider that, so I'm already very limited to these medications that are approved for kids. You know if I had a different population I could prescribe the off-label medicines. I just feel so limited by that, working with the Medicaid population and again, private insurance will pay for anything I put on prescription, they don't care about that." In addition, another clinician stated, "The first-line treatments that their Medicaid plan covers, we still have to start with trying them. You know, there's no point giving testing to everybody who walks through the door."

Most clinicians found it to be frustrating that insurance would only cover medications on their formulary despite pharmacogenetic testing results. Another major concern was the cost of L-Methyfolate or Deplin supplements. The pharmacogenetic tests provide results on folic acid conversion which is a supplement that has shown to improve depression among certain individuals who have a deficiency and need supplementation. One clinician stated, "Yeah. I do think that there's some risks. That is, you know, like with the folic acid conversion. What's the use of giving them the information and then that they can't afford \$40 or \$50 every two weeks, every month of this supplement. It's not really conducive to do it or even to talk about it."

Similarly, another clinician reported, "I've not had the. unfortunately I've not had the advantage of treating a lot of patients recently with Deplin because it is considered a medical food. And a lot of the patients who I treat have what we call PeachCare in Georgia. It is sort of like state funded program quasi- Medicaid. It's sort of like a Medicaid but for kids who you know parents make too much money to get Medicaid but not enough money to get private insurance, sort of like that. So, you know so the cost

unfortunately is a limiting factor for many people or just accessibility to Deplin. So, when I was in private practice I had the advantage of having pharmaceutical reps you know frequently coming into the office bringing free samples, so we had a rep who brought Deplin. So, you know I would often -- you know if I had someone who came back with significantly reduced conversion I would give them samples of Deplin to try. And many times, they would you know start to notice improvement particularly in depression symptoms. And so that was sell them on the fact that it was worth you know spending their own money out of pocket to buy the Deplin if their insurance wouldn't cover it. Well, the downside to all of my patients, or not all, the downside is the majority of my patient having Medicaid and Medicaid CMO's that it's difficult to get them to pay things like Deplin. But the upside of it is that for those patients there is no out pocket expense for the testing for GeneSight ...so they pay nothing. GeneSight is totally free for those patients." Clinicians found that even with appeals, insurance companies still do not pay for the L-methylfolate supplements such as Deplin. Many clinicians thought it was ironic that the insurance company would pay for the pharmacogenetic testing but were not willing to pay for the supplement if it was indicated for the patient.

Cost of Pharmacogenetic Testing

The cost of pharmacogenetic testing was considered a major downside of the test for most clinicians in the sample. One clinician stated, "I don't order it as a matter of routine on a new patient. Because it's you know, it's stopped by costs and you know, honestly, I think you should. I think everybody should have genetic testing done." Clinicians were less likely to order pharmacogenetic testing if a patient did not have insurance.

However, cost was still a barrier for some clinicians even if patients did have insurance. For example, some clinicians found that some insurance plans only covered genetic testing for a specific diagnosis which may not apply to their patient. One clinician stated, “a concern for me about the testing where sometimes I think, it’s a challenge from a clinical standpoint is that, some of the testing companies require specific diagnoses for them to bill to insurance companies. Medicare only covers the test if there is a depression diagnosis.”

Additional clinicians found that patients were receiving “explanation of benefits” from their insurance company revealing astronomical prices for the test and this caused a lot of anxiety for the patients. One clinician stated, “The only risk is financially where a lot of the patients before they get anxiety because they get a bill in the mail from the company which is like for \$16,000 or something crazy like that. And they call the office in a panic and I always try to explain them at the time that I do the test. I found that it’s just a declaration of what their benefits cover. As far as their insurance company, that it’s not a bill. But I’ve had some cases where they actually send the bill to the client. And then I have to call the company with the client in the office and they’re in a distress mode and work out the billing situation with the company over the phone. And in all cases, it was resolved, but there’s still the inconvenience for me as the clinician ordering it. There is also is a stressor for the client.” Another clinician stated, “sometimes people are getting bills in the mail of \$6000, \$7000 for the whole panel and they obviously see a lot of Medicaid and Medicare clients and that’s almost a year’s income for them for a test. So that’s a very distressing you know event for them. But sometimes for whatever reason, they don’t process the insurance properly or something happens and the people don’t still

get a check or a bill – get a bill in the mail, it’s still very distressing.” Although, the cost of the test was corrected for these patients, the clinicians found the process time consuming and distressing for the patient.

Most clinicians agreed that they would not order the test for patients who do not have insurance since it can be several thousand dollars for cash pay patients. In addition, some clinicians believed that the co-pay for commercial insurance may be too expensive, which can be up to \$330 for some tests. One clinician stated, “Now that I work with mostly Medicaid/Medicare, I use GeneSight, but you know it’s \$330 at least typically for a co-pay for commercially insured patient. So, people are just, you know they, again I’m not selling it as a perfect science and I encourage people to do it, but not everybody wants to spend that much money on it.” Clinicians found that some people declined the test because they could not afford the “bottom line”.

Misinterpretation of Data

Misinterpretation of data was identified by clinicians as a major downside or risk to pharmacogenetic testing. Clinicians were concerned that patients would have a misperception of the results, unrealistic expectations or clinicians would misinterpret the results. In addition, clinicians had significant ethical concerns about the test.

Perceived results. Clinicians were concerned that patients would perceive the results differently. For example, one clinician stated, “I think if the genetic testing is not carefully explained to patients, I think there could be, there is a risk for misunderstanding, misinterpretation of what the test actually tells people what it means.” Another clinician stated, “If they feel like its diagnostic or if they feel like it’s a dictate on what’s a medicine that they should use based on how it’s presented.” Similarly, one

clinician stated, “I think if a patient is led to believe that it’s a perfect that they can somehow find a perfect remedy by taking the test then that would certainly be a pitfall.”

Unrealistic expectations. Some clinicians were concerned that some patients may have unrealistic expectations of the results. One clinician stated, “A downside might be if patient that's like they are overly – has a unrealistically high expectation of you know how it will help them – but really that's probably the only thing and that's where you're you know good patient teaching comes in. I haven't really had that issue, but I can see how that could happen.” Another clinician reported, “I think if a patient is led to believe that it’s a perfect that they can somehow find a perfect remedy by taking the test then that would certainly be a pitfall. But I think that’s really up to the provider to ensure that accurate education is given on you know the nature of the test as well as its limitation.”

While other clinicians were concerned that clinicians were not interpreting the data correctly. For example, one clinician stated, “Only downsides I can see are misinterpretations of what the testing actually represents. Might be a medication in that red category that is the most appropriate medication for them but just with dosing adjustments, might be a significant consideration and that including, going above what would be considered an on-label dosing if they, if it’s indicated.” Some clinicians were concerned that others may not utilize the data by making appropriate dosing changes if indicated by the test if they interpret the “red column” as a “no-go” column and only use medications listed in the “green column”.

Ethical concerns. Many clinicians believed that some patients may be fearful that their DNA data would be misused by insurance companies. One clinician stated, “I mean

there may be down the road there are some issues with the testing results and the genetic stuff being misused by government or insurance or something but I suppose that is true of all the genetic substances accumulating.” Another clinician stated, “ I think in their insurance perspective as far as if information could be used or disseminated to insurance companies, which I know it from my understanding isn’t and can’t be. Then that could potentially provide insurance companies with the reason to not insure, have different rates based on certain genetic marker results. That would be a sort of a macro societal risk but for the individual, that would obviously impact them too. Just I guess a little bit about what I was saying earlier with regards to potential misuse. I would perceive this misuse of the information by insurance companies trying to find out more genetic information about patients so that they can kind of risk, stratify their patients and charge higher rates on certain people that may not be “good metabolizers” in term of person.”

However, another clinician found that the patients do have an option to have their DNA information destroyed after a specific amount of days if they are concerned about misuse of data. This clinician stated, “one of the things I like about this test is it gives the client the option to have their sample destroyed within 90 days, but I think kind of, I mean that’s just empowering to be able to say, I don’t need to do anything, but tell me my test and then you’re going to destroy my sample. So, I think the risks are more kind of those policy type issues.”

Another major ethical concern of pharmacogenetic testing was how the patient may internalize the test results. One clinician stated, “I think so, I think it, I used to not think this but I think that our minds are so powerful and even like my like analogy of the hazmat suit I think it’s psychologically, I am starting to like rethink that like you really

want to talk to someone with a hazmat suit on or do we want to stress the epigenetic more, you know? So, I mean even though like Genomind has the calcium channel ion test and you know and just from my perspective I found that people are more of Bipolarish with those Mets especially if they present with the mood instability. But I mean how do you explain that to just like where they go, do you just use it for prescribing purposes? I mean, I guess there are some questions are ethics that come in and turns of this is new science and it is so much more important than any genetic vulnerability that you have to be careful.” Some clinicians were concerned about how to explain the results and how the results may affect the patient psychologically.

Minimal or No Risks

Although several risks or downsides of the test were identified, most clinicians agreed that that pharmacogenetic testing had minimal or no risks to the patient. Many clinicians commented that there are no physical or medical risks since the test is a buccal swab and does not require a blood draw. One clinician stated, “You know, I don’t really see a downside, especially when it comes with their Cytochrome P450 pathways. I don’t see where a negative thing could happen you know knowing that you’re a poor metabolizer of 2D6. No immediate health risks. Like I said it’s a buccal swab.” Another clinician stated, “I don’t see anything physical I think the emotional risk is getting affirmation so that’s a good risk I think.” Additional clinicians explained that as long as the patient understood the costs and that the test is “not an absolute that there’s no guarantee that this is going to be the most effective medication that if it’s explained to them that this is yet another tool among many to come up with the right medication for them then there is not really a risk.”

Patient's Perception of Pharmacogenetic Testing

Approximately 89% of clinicians in this sample agreed that patients understand that usefulness of the pharmacogenetic testing. However, most clinicians believed that the patient's understanding depended on how the provider educates the patient. One clinician stated, "I think I've never, it's rare that I have somebody who has unreasonable expectations of what it can do. Occasionally I will and those tend to be patients just with a little lower education level who just maybe need more counseling and you know more repeated explanations to more fully understand it. But I think patients generally get the idea of it." Another clinician explained the process as the following: "Most of them get it immediately, no matter what their educational level they get that, it's like it being a super sleuth you know. And we're looking for more information. So, I think I'm being a little scientist or a little detective and you know I can be there with them, or we can look for as much information as we can possibly get to solve the mystery of who they are, and why they are presenting you know with symptoms that they have. So, they get that and I think they understand that. In fact, very often, I mean I don't know how they perceive it but very often they'll come back and they'll say could my family, a family member being tested." Most clinicians found that patients had a basic understanding of the test as long as the clinician took adequate time to explain the test and results. According to clinicians in this sample, several factors that affected the patient's perception of the test included patient "buy in", perceived effectiveness, and patient education.

Patient "Buy In"

Clinicians believed that beyond the scientific aspect of the test, that there was a psychological aspect that influenced patient's "buy in" to the test. Several clinicians were

surprised at how receptive patients were of the test. Clinicians believe that pharmacogenetic guided treatment increases patient “buy in” by giving patients hope and confidence.

One clinician stated, “Patients generally respond to it well, they like doing it. It gives them some objective data to look at instead of just being so abstract and taking the medicine that they never heard of that they hope will help. So, you know they get a copy of the report they can look at, go through it. I think sometimes just having a patient have that in their hand and some objective data, it helps them have some hope that it will work.” Similarly, another clinician stated “I think a lot of people think that psychiatry is a lot of the guessing games, type of thing and we can get any more exact science to what people are experiencing, I think it makes them a lot more trusting in what we’re doing.”

Another clinician stated “So in this kind of situation like I said quite honestly, I feel not just for me in terms of my decision making and my medical recommendations. But I feel like it also gives the parents some level comfort I don’t know if that’s the right word necessarily. But it gives some level of comfort or confidence that you know we’re hopefully going to be choosing from a more limited number of medications and hopefully for medications that are less likely to be ineffective and less likely to cause side effects.” Another clinician agreed and stated, “I think, I think there is a couple of things that come in and the play with the patient. I think number one, if they have a higher level of confidence that they are not going to have side effects I think that plays into it a great deal.” Similarly, another clinician reported that the test was “not always a 100%, but it can kind of build the confidence in the patients.”

Patient “buy in” was a major factor of a patient’s receptivity towards pharmacogenetic testing. According to clinicians most patients were satisfied with the results and were excited to have something scientific and concrete. Clinicians found that a written report helped provide hope and confidence to the patients about the clinician’s treatment recommendation. Most clinicians agreed that the patients had a basic understanding of the genes and what medications would work best for them.

Perceived Effectiveness

Clinicians found that how well the patients perceived the effectiveness of the pharmacogenetic testing impacted their outcomes. For example, one clinician stated, “I’m a big buyer into the pharmacogenetic testing because of the perceived effectiveness of it. But right about 10% of the it that I order it is I would say is very effective the other 90% I would say is not really clinically that relevant. And I don’t know, you know, it’s my personal experience that if a medicine that’s in the green column and the person has not tried it before and I tell them about the science behind the test. I don’t know whether or not that’s the test working or if it’s the placebo effect that we said first. I feel like their buy in is a little bit more, this is the scientific thing. I would count that as worth something”

While another clinician stated, “I will say though with some parents, I feel like in some ways it has a little bit of a placebo effect. That they like the fact that the test and that’s something comes back with this report. And so much of mental health is not objective like that. And there are some parents where I feel like they maybe it didn’t help me a lot but it gave the parents that comfort and a belief that this medicine that was picked. It’s going to be good for the child even though I totally explain that we’re just

looking how they metabolize the medicine not really the therapeutic effect of it, even though I've explained all these I feel like they will latch on to it and kind of have a positive view and if that makes any sense.”

Several clinicians mentioned the “placebo effect” of the test. Most clinicians agreed that there was a psychological component that this was a significant factor in the receptivity of the test. Some providers were unsure if the test was completely accurate or if it was the presentation of findings that resulted in positive outcomes among these patients. However, many clinicians agreed that the patient’s “buy-in” was worth it and patients did not feel like the clinician was just “throwing medications at them” but it was more of a scientific decision.

Patient Education

The majority of clinicians in this sample believed that patient education was a significant factor in how well the patient perceived the test. Some clinicians thought it was best to keep the explanation of the test simple, while other clinicians believed that the patient would benefit from a more detailed explanation of the test. Clinicians found it helpful to explain the benefits of the test and also the limitations of the test. One clinician stated, “I start out by explaining to them that the testing is not going to be a definitive tool. There is not a way to interpret that says just because you can metabolize this medicine normally and there aren't any genetic variations in that, that it's the right medicine for you. Explaining to the patients from the outset that we're not going to get a definitive direction on medications from the testing has been helpful.”

Keeping it Simple

The majority of clinicians in this sample believed that the clinician should educate the patient in simple layman's terms for the patient. One clinician stated, "I try not to be overly technical about it, but at least letting them know based on their own genotype what medicine might be more or less likely to respond to and what cautions we need to be aware of. Like for proceedings with certain ones that may be better lower doses or higher doses or might be more prone to the side effects."

Another clinician stated, "And as far as metabolism, I don't really go down that road." Similarly, another clinician explained that test as the following: "I don't go into every single gene, I don't think that's helpful to most patients. I mean occasionally there are patients who are in the medical field who want to discuss in further detail and we certainly can do that at their request. But in general, I just try to I explain the overall you know idea of the fact that it's, it is taking, we're getting a sample of your organic materials, that the lab can analyze these different genes and see how well they metabolize different medications. And then create the profile that can be helpful for us to guide us in the right treatment decisions."

Most clinicians found the GeneSight test easy for patients to understand. One clinician stated, "Well, I mean, the results are pretty easily interpreted. The GeneSight made the medications in green, yellow and red column which they can somewhat understand. I mean, it's a little more complicated than that. At least it's something they can look at and understand. If this is in the green column it's more likely to work and has good results with less side effects. And then whether there might be some interactions and there's some smaller and moderate risk that the patient won't tolerate or potentially

have side effects from the medication is kind of like the yellow-light. And then medications that are very prone and more at risk and probably should be considered either and not to be used at or be discontinued if they are the already on and that would be more of a red-light scenario. So, everybody can kind of use that visual and the results of the tests are set up and three columns or it's pretty easy to understand now."

More Scientific

However, other clinicians believed that a more detailed explanation was necessary for patients. One clinician stated, "So, it could be pretty arduous task to explain it, it's very complex ideas them but I think you have to try and so anyway. But for the most part I've have good success. I have been pleased with the results."

Another clinician found it important to explain the metabolism of medications, by stating, "I explain to them what that means that either their liver creates certain enzymes that specifically send certain chemicals to break them down and so that they be eliminated from the body and that some of them work more efficiently than others. And I try to stress to them just because they have, you know, a poor metabolizer of a certain kind of enzyme. It doesn't mean it doesn't work at all. It's just means that it's not as, it doesn't do its job as efficiently as the one we usually, the normal one if you will. It works too well, you know, as an ultra-metabolizer, you just, it's a worker bee it works so hard the medicine never actually gets into the bloodstream. It breaks it down before it ever gets circulating in the body, things like that. But, I go through and tell them what that means you have a higher risk for this or a lower risk for this but it doesn't mean you have are immune to it but you have a lesser risk."

Knowledge Gap Among Clinicians

Few clinicians stated that they do not understand the all of the scientific aspects of the test. One clinician stated, “I do my very, I just do my very best to keep it as simple as possible. And I do go over every single page and I say if you want to know real scientific stuff about it I said you probably just have to call the lab and see what they have to say.” Some clinicians found that most patients just want to hear which medications to take and which medications to avoid.

Similarly, another clinician stated, “The phenotypes, the genomes makes me a little crazy so it's a little over, out of my league so I don't, I don't go over it, I don't pretend know it all everything that's on the test. Just getting to the basics.” An additional clinician stated, “Now some of the other stuff, you know, the CYP pathways I don't even understand. They probably don't either. But I tell them, if they want to call and get more information, the number is on there and just to call.”

Overall, there are different education styles among clinicians which may affect how a patient perceives the testing. Some clinicians prefer to explain the test in layman's terms while others prefer to provide a more detailed explanation. Few clinicians reported a gap in knowledge regarding the scientific aspects of the test. Some providers choose their education style depending on the education level of the patient and their intellectual ability to understand. Some clinicians discussed test results in just a few minutes up to one hour depending on the clinician. Most clinicians reviewed the test and the patient's previous medication trials before going over the test results with the patient and provide the patient with a copy of the test results. Despite the different education styles, most

clinicians were confident that patients understood the applicability of the test and were favorable of the test.

Application of Test Results Among Clinicians

Clinicians in this sample found pharmacogenetic testing to be applicable to patients with a variety of psychiatric disorders. Many clinicians reported that the test helps to identify problems with medications, helpful with prescribing and augmenting medications, and reduce trial and error among patients. Clinicians in this sample identified how they are using pharmacogenetic testing in current clinical practice to guide treatment decisions through medications in adults and adolescents with the multiple psychiatric disorders.

Medications

Clinicians identified several ways that pharmacogenetic testing was helpful in selecting and dosing medications. One clinician stated, “I just guess picking the medication is sort of like finding a needle in a haystack I think of the testing as we’re moving a lot of the hay.” Clinicians were more likely to go higher or start lower doses of medications depending on test results and metabolism differences. Clinicians used the test to help them identify patients at risk for weight gain or side effects, inborn metabolism issues, dosing medications, and the impact of the test on patients taking medications that are structured similarly. In addition, many clinicians reported the benefit of the Methylenetetrahydrofolate enzyme in this patient population.

Weight gain, inborn metabolism error, and side effects. Clinicians in this sample were able to use the pharmacogenetic testing to reduce side effects and improve tolerability of medications. Some clinicians reported that it helped them to identify if

someone was at risk of weight gain or side effects from certain medications. For example, one clinician stated, “With the long and short form of the serotonin transporter and then that variation at the 5-HT2C, you know I’ve had people tell me about weight gain and certainly the results of the test to forward that yeah, they are more likely to gain weight.” Clinicians used this information to reduce weight gain in these individuals.

Additional clinicians found the test to be helpful to identify if a person had an “inborn error in metabolism” that would affect their responsiveness or tolerability to medication. For example, one clinician stated, “x and y medications and the black box warning on Lamictal and the mood stabilizers it can direct on guidance in terms of knowing if someone possibly has an inborn metabolic issue that would affect their responsiveness or side effects profile to medication.”

Another clinician stated, “I had a lady. She was taking Paxil which I don’t like prescribing Paxil anyway because they tend to have a lot of side effects. But it’s an older Selective Serotonin Reuptake Inhibitor and she was saying whenever she took that medicine, she had brain shocks where she would feel like electricity was running through her brain. That Paxil is the type of medicine that once you stay on it, it’s hard to get you off it because you get the withdrawal. She was very afraid to withdraw off that medication, so she never stopped it. So, we did the genetic testing and I was able to convince her that with Paxil is listed here in the red. And we got her off that medicine. We started her on another medicine which was in the green which was Effexor XR or Venlafaxine she did a lot better.”

Dosing. More specifically, clinicians identified several success stories of different medications and how the test guided their treatment decision. For example, one clinician

reported, “I’ve had a couple of really fascinating cases one involving a pair of identical twins. We did the testing on both of them and they came out identical. (*laughing*) Which was really interesting. You would sort of hope that would be the case (*laughing*) but you never quite know when you’re onto something. But one of them had some kind of genetic variation or something like that. And in their cases, they both tend to take high doses of the same medication actually and based on the genetic testing it kind of showed... no wonder they’re taking high doses because the testing was sort of indicating that they just might need to do that and that was very interesting. I also had one instance, and not too long ago, where I had siblings where both siblings had testing done and it was as though certain aspects of it were identical, and other aspects which is completely different.”

Another clinician reported, “I have one lady that we had her on 120 of Cymbalta. And by the time she had taken the test, we changed her to something else. Well, we got the results, she that’s why the 120, still didn’t even work, you know, whichever it is, slow metabolizer, so therefore, for fast metabolizer, therefore, needed more. That’s why it didn’t work.”

Similarly, another clinician stated, “Well, I mean I’ve had a number of patients who were you know creeping up towards the higher end of dose ranges on certain medications and if they had testing done and it came back and indicated that this patient might need higher doses, then that was really helpful because that way as long as you were tolerating it okay, you felt a little more comfortable about going up towards that high end of a dose range and maybe even certain instances going a bit above it.”

Similarly structured. Clinicians also found that patients may metabolize differently two medications that are similarly structured. One clinician stated, “What I think was so fascinated too is about is that you can do the testing let’s say you’re on antidepressants and a patient will have, let’s say, Lexapro in the green category and Celexa will be in the red. It’s unbelievable, one is half the molecule of the other and with Pristiq and Effexor they can be so different and I try to point that out to the patients and it’s really amazing that it could be detected, that kind of a difference for medications that aren’t that structurally different from another.”

Methylenetetrahydrofolate enzyme. A majority of the clinicians found the Methylenetetrahydrofolate (MTHFR) Enzyme information from the test to be very helpful in treatment. Clinicians discussed how MTHFR is a precursor to neurotransmitters and can affect depression in many individuals who have a significantly reduced folic acid conversion. One clinician described L-Methylfolate as a “magic wand” and stated, “So, with the folate it’s seems like with this l-methylfolate is like this magic wand (*laughing*), you know is like okay successfully the body is better able to receive the chemicals where they need to go. And so, when I have people who are really, really lethargic I think about a lot of things. But I mean folates one of the things to think about, I think about B vitamins. I think about a lot of things, but I also will just start them on a low, low, either medical food like Deplin or an over the counter. And so that’s kind of how I educate them about the L-methylfolate, and just to you know we only make one change at a time, so I don’t, I don’t change their medication, and some other nutritional thing and that folate, I’ll tell them just how to try this folate, for a week or two just begin

to just notice, some people notice that right away, just wake up the next day say oh my gosh my brain is working, you know I can concentrate.”

Another clinician stated, “Well I have actually just, I have one patient who only takes the supplement and she does significantly better. She also was able to, I don’t know if this is related at all, but she was able to stop smoking pot which she had been smoking every day. And she, and so I don’t, she thought it helped her get off marijuana so, but she and I did have her on an anti-depressant. Eventually I was able to just stop the anti-depressant without any resurgence of symptoms whatsoever.”

Similarly, another clinician stated, “Occasionally, I’ll see someone where it’s pretty clear that they don’t need medicines and then they don’t get the test except for maybe the MTHFR test. Yeah, I think it’s beneficial because we’ve known for maybe 20 years or so that some patients particularly those with depression don’t respond very well to antidepressants unless they had supplementation with L-methylfolate and the people that need L-methylfolate are the people on the testing who fall either in the far right or middle ranges as opposed to the far left, which is normal. So, I find that probably how about equal numbers of people are on the far right or in the middle, excuse me the far right or the far left. And then a whole lot of people are in the middle and so I would say about two thirds or something of the people that I tested I find an L-methylfolate supplement. And I think it helps.”

Most clinicians in the sample found the MTHFR information to be valuable information from the pharmacogenetic test. Clinicians reported that patients with a L-Methylfolate deficiency are at higher risk of inflammatory disease including hypertension and cardiac problems. However, some clinicians stated that they did not use this

information often in treatment due to insurance not covering the L-Methylfolate supplementation and the cost was a barrier for many patients. In addition, some clinicians reported that they were not convinced by the literature that supplementation was beneficial. One clinician stated, “I don’t really know much about that literature actually. My understanding is that there is some debate whether that folic acid information is actually a helpful. In the actual clinical setting that you do have to be severely folate deficient in my understanding to benefit from it.”

Adolescent Population

Clinicians in this sample found pharmacogenetic testing to be beneficial in the adolescent population. Some clinicians were more likely to “think outside the box” and look at alternative medications that they would not necessarily consider after using pharmacogenetic testing. One clinician stated, “Typically you know SSRI’s you know more well studied in young people or in many not all that do have FDA indications in minors. And you know, so just classically you know have always, not always but majority of the time you know use SSRIs first line for both anxiety and depression and anyone under the age of 18 as opposed to an SNRI Wellbutrin or something. And so, having done this testing has sort of opened my eyes to how many people are likely be co-responders to SSRIs because of the serotonin transporter. And so I’m sort of considering non-SSRI medicines probably early in the course of, earlier in the course of treatment now than I would. But certainly, has been beneficial to me in terms of you know helping steer my prescribing practices in a direction that I think is more beneficial to my patients. Often times go ahead and ordering the GeneSight testing, so that I’ll know okay is the

second SSRI trial worth it or should I just move on to an SNRI or Wellbutrin or something like that.”

Similarly, another clinician stated, “Well, there is one girl, she’s just an adolescent. She’s maybe 15 and her mom is super, super anxious and she’s depressed and anxious, the child is. But the mom is very anxious about medicine and I tried like two or three SSRIs with her. And she would have these like one of them she felt like it made her suicidal and then when she would just have that seemed to me to have extreme side effects whenever it was she felt weird or, or her stomach hurt but it seemed kind of extreme. And so, I finally suggest that the test and it actually did come back, that she did not metabolize a lot of those as well. And there was one kind of left on the list that she could metabolize on this list like Zoloft and then all of those new ones that are not approved for kids. So, to be honest I’m not sure whether it but she’s done better on the Zoloft, she’s been willing to take it and she has done better. And I don’t know whether it’s really because she tolerates that or they just believe so much because they really liked getting this report. But doesn’t really matter to be because she’s taking it and she thinks she’s better.” This clinician was unsure if the test was accurate or if the patient was doing well due to a “placebo effect” of the test, however, the clinician was pleased with the outcome.

In addition, clinicians found that parents were eager to have the testing done on their children. One clinician stated, “Parents are looking for something for their kids. They want like some they want the best. They want the newest. It’s my kid, I got to give this big job, and so sometimes parents are really eager sometimes.” The same clinician discussed how “A woman was given the affirmation that she was right and the doctor was

wrong all those years and she's in her 60's, you know maybe 50's and she has been receiving psych care for since her 20s.”

Another clinician found that the testing to be critical in adolescents who were suicidal to reduce trial and error. This clinician stated, “So but I did get to 17-year-old and I have one that even I had a male come in a while back he was having transient suicidal thoughts I did the GeneSight and that was the first thing we did was the GeneSight. Because I feel like that is extremely serious situations they're much higher they are high risk for suicide you and I just don't want to play around with medications in that kind of situation. Plus, their naïve to medications, we can do several trials you know and waste a lot time I thought it need to be addressed right then.” This provider believed it was crucial to order testing to find the best treatment possible for this adolescent.

Autism and Non-Verbal Patients

Clinicians in this sample found pharmacogenetic testing to be beneficial in patients with autism or those who non-verbal. One clinician reported how she was able to identify a reduced folic acid conversion in a patient with autism and responded well to treatment. This clinician stated, “I had a new patient who had been treated in New York always only by a neurologist never a psychiatrist. And I think she was one of the ones that walked through the door for the first time that I did genetic testing on her because she's on the autism spectrum and a lot of the times they don't respond the way you want them to the medication and I thought I'm not going to just start guessing. I'm going to do the testing and see what it comes back as and she came back, she came back deficient and so I gave her, we had samples of Deplin, and I gave her a couple of boxes of samples. And mom was like I see the difference and they can't afford it.”

Additional clinicians discussed how they have found pharmacogenetic testing to be helpful in patients who are non-verbal. One clinician stated, “I have one client who is or he is in his probably late 20s and he is developmentally delayed and severely so he is non-verbal and his mother has been struggling to figure out what to do for him to calm down. He gets agitated playing about he can get, he can violent and she couldn’t find the right kind of medication for him and so she came, he came to my service after being around about the time or two. And I started, I told I started off by saying that why don’t we try this and she was you should have still look on her face. She is just is like oh my gosh this might be the miracle answer. And I reassured her might not be the miracle answer but it’s another opportunity to approach his behaviors in a different way with the different kind of medication because maybe, you know, maybe it’s time for a change. So and I think that’s the main thing that makes me try it again and again and it’s the fact people see some hope for progress with themselves or their kids so. I usually order it on patients who are having some kind of what, two, two kinds of patients. First it will be non-verbal patients, I take care of a number of group home patients who are nonverbal. And I’m looking for any, most of them have been living in a group home, behavioral episodes, they are on six meds. They come to me and I try to get any kind of input I can get.”

Similarly, another clinician discussed how he was seeing a “non-verbal 21-year-old was given a stimulant he was taking a lot of that, a lot of Adderall and just wasn’t comfortable with the dosing amount that he came to me. We did the testing, the testing showed he was fast metabolizer and that gave me more comfort to write for that med, the dose, doses.”

Clinicians discussed how it can be difficult to treat patients who are non-verbal since they cannot tell you what is bothering them. The clinicians reported that they rely on the caregiver and their exam of the patient. Clinicians reported that the pharmacogenetic testing provides another tool to help guide medication selection in this population.

Addiction Disorders

Some clinicians found it helpful to know if a person was a slow or fast metabolizer of medication in patients who had addiction disorders or co-occurring disorders. Clinicians reported that the test would help them to determine if they were drug seeking by asking for more medication or if they were truly a fast metabolizer and required higher doses. One clinician stated, “For the substance abuse population, it's been helpful. To say hey, look, they will come back asking for more. This is how your body says you metabolize medication. That's been helpful from I think the psychological state of I need more, it's not working, I'm still having cravings et cetera, et cetera. So, it's helped me in that fashion to have some scientific literature to say hey, look, it's not a rationale to say that you would probably need to go with more or actually you need to be lowered, actually they could be split into your dose because you metabolize it too fast. So, it helped me to have that scientific support to say that and give them a copy of it to establish more of a common relationship and to say look, try to understand what I'm understanding my rationale in this decision-making here.” Clinicians found it helpful to have a scientific report and rationale for their decision.

Attention Deficit Hyperactivity Disorder

In this sample, clinicians had conflicting views about the usefulness of pharmacogenetic testing in children with Attention Deficit Hyperactivity Disorder (ADHD). One clinician found the test to be useful in a 9-year-old patient who had a disruptive mood dysregulation disorder and ADHD. The patient had not responded well to any medication and symptoms were not controlled. The clinician ordered pharmacogenetic testing and found that the patient does not respond to 99% of psychotropic medications. The clinician reported, “As of when I saw her earlier this week it helped me try to make a couple of changes and we started with the medications that gave the longest time to see any kind of effect. And just when, on Tuesday when I saw her just decided let’s change the stimulant because we haven’t been able to get the mood regulated. Let’s at least try to get her focused on for school. I haven’t had any phone calls yet, which is unusual...so it might have helped.”

In contrast, another clinician stated, “I had a kid who he was, it’s Concerta, was in the red category for him and supposedly for him per his mom and the teachers it was, it was really, really effective. But it should not have been because he was, he was supposed to have a reduced response on alpha receptor and on COMT so it was in the red category for two different reasons that basically he should not well on any stimulant. And he also, did not, was not sensitive to alpha so, and the alpha receptors. I couldn’t exactly, I couldn’t explain that scientifically if I wanted to but needless to say the reality was he was doing well.” Therefore, this clinician did not change the dose or medication since the patient was doing well. However, the clinician did state “I don’t see that a lot”. However, the clinician could not explain why the patient’s report did not match the testing results.

Anxiety Disorders

Some clinicians found pharmacogenetic testing beneficial for patients with anxiety. Clinicians reported that patients with anxiety are usually anxious about taking any medication and the test can increase patient “buy in”. One clinician stated, “So if I have a patient that comes in, very anxious OCD type and they had a reaction to one SSRI. Then sometimes, I use it more for patient buy in. Because I'm like well you know this test is a more objective way to let me know what your response would be, so that's one. And then if I have patients who have become just very resistant to a lot of drugs that gives me a place to start.”

Another clinician reported how the test was able to guide dosing for a patient with anxiety who was experiencing side effects from a medication. This clinician stated, “So one example would be an older woman who is in her maybe late '60's, '70, who had multiple failures. She keeps saying she thinks she is not for depression but anxious, but she presents as depressed meaning she fires the pancake, no energy, and you know. But she does, she says I want you to treat my anxiety because is that is what is worries me, my panic, my agitation. And she's been a sort of a, an enabler all her life and you know she gave energy away, and so it's more of the behavioral really than it is medical. But she, but then she doesn't want to look at that. (*laughing*) So she wants a magic pill right. So, she has now many, many, many medications and she's been in and out of day treatment programs, hospitalization. And so, we find the advantage to this so try Trintellix her because it does so many things you know lifts the depression, calms the anxiety, and helps with focus and concentration and help with the energy like needing the cognition and then feeling more energized. So, I convinced her to try that, and she

started doing a little better, but then she became more activated and agitated as we were going up on the dose, and this has been her history that she did this thing whenever the doctor would go up on the dose she would get more agitated. So, what we did, we got her test done for gene test done and I had the test results the day that she called us that she was getting more agitated. And so, we opened the gene testing, and in her case, she needs a lower dose. And so, instead of increasing the dose, I just said break that pill in half, and just take that a half a pill, and then let's see what happens. And she really kind of got stable after that time minimal medication now." In this situation, the clinician was able to change the dosing of medication to improve the patient's outcome.

Depressive Disorders

Some clinicians found it helpful to look at allele changes in patients with depression to guide their clinical decision-making. One clinician stated, "Evidence pretty strongly suggest and supports depression tests to make sure that they will respond to SSRIs. But they have that short form not to use an SSRI and to go with an SNRI, SNRA, you know something different. So, I think we're starting to see more evidence for some of the other allele changes for some of the pharmacodynamics things, but not enough duplication in the studies yet to definitively say yes, these results, means you should do this. I think right now outside of depression it's more of a loose guideline that might steer you in the right direction, but it does not necessarily mean do "x", do "y"."

Similarly, another clinician stated, "But she had been tried on two or three different SSRIs for depression and anxiety since a teenager. And I said yeah let's do some genetic testing with you and I did and it turned out she had two short genes on her serotonin transporter. So, you know it was typically indicating more, might expect a poor response

to serotonin medication so which kind of proved why she had not done well on the three SSRIs and I put her on Wellbutrin.”

Another clinician found the pharmacogenetic testing was helpful but more helpful in conjunction with other therapies. This clinician stated, “I have one patient who basically had failed everything and every combination of everything and I’ve been trying for years to help her with her depression. And she was like the first person I did use the test on because she was suffering so much and had such bad response from all these things we tried and it still didn’t. So, you know using the medication from the green category, she still does not go into remission. So, it wasn’t actually until, it wasn’t actually, until I really bumped her up out of the normal dose range and combined it with a typical and Alpha-Stim. I started using Alpha-Stim for, and that's the combination of all the above and it would just be enough to tip her into remission.”

Schizophrenia

Several clinicians reported that pharmacogenetic testing often confirmed why medications were ineffective in patients with Schizophrenia. One clinician stated, “I find especially with my patients with schizophrenia that the test just confirms while nothing is worthwhile, nothing is working, because they have a full or partial deletion of the dopamine 2 receptor. And so, then it usually, especially they have that history of failing multiple antipsychotics that as we know most of them have the high affinity for D2. Then I will try to give them to where it’s something that has like Clozapine or Prolixin that has higher affinity at D1 and D4. You know, I try to think about a different way to approach their illness.”

Another clinician stated, “I have found it helpful recently, well I had a girl get the testing because we’re trying to see which neuroleptic medicine for her schizophrenia. She was having side effects and it came back and said that basically that she was the slower metabolizer and she was more likely to get side effects and needed lower dosage. Good to know because cause when I start these meds, I started the lowest possible dose. And she went to the hospital, they increased it a little bit she was having side effects so we had to drop it back down, so we’re going to increase it very slowly considering that I know the genetic testing. I actually send a copy to the hospital with her but I don’t think they looked at it.” The clinician reported that the patient tolerated the medication at lower doses and found that it was not helpful when the clinicians in the hospital did not take the test into consideration.

An additional clinician stated, “So, her primary care provider was prescribing simvastatin for her and so her diagnosis that I was treating her for was paranoid schizophrenia. And she is a very complicated patient in that she is a polio survivor and she’s in a wheelchair every time she comes to see me. Although I think she can stand because she’s does use her legs to move the wheelchair. Anyway, she has a history of LSD usage. And she was telling me that every evening about 6 o’clock in the evening, she would start hallucinating, visual hallucinations, like she was on an LSD trip. With flashing lights and it was very uncomfortable for her. So, she’s been on all kinds of medication. She was on Haldol which I really didn’t want to see her stay on because I was beginning to learn about the neurotoxicity of Haldol. So, I did the pharmacogenetic testing to find out which meds would be best for her because I was intending to switch her meds. So, when I discovered that she doesn’t metabolize simvastatin properly and the

debris from the metabolism collects in her tissue and it can clog up her kidneys. I notified her primary care provider and immediately took her off of the Simvastatin. And within weeks, the hallucinations she had everyday stopped. So, I believe they came from the abnormal metabolism of the Simvastatin. So, with this one test, I can determine if there any abnormalities in her genetic structure that would affect the medications for those different diagnoses.” Clinicians found pharmacogenetic testing to be helpful to reduce side effects and increase tolerability of medications in patients with Schizophrenia.

Clinician Recommendations

Clinicians in the sample found the test to beneficial in clinical practice. Despite the benefits of the test, several clinicians suggested several recommendations to improve the practicability of the test. Clinicians recommended test affordability, test expansion, online access, patient education materials, and a more efficient ordering process and turnaround for test results.

Test Affordability

Most clinicians found that most government payers provide adequate coverage for pharmacogenetic testing. However, commercial insurance or cash payers may not be able to afford the pharmacogenetic testing according to most clinicians in this sample. Cost is a major barrier for this patient population. Although most pharmacogenetic testing companies provide an income-based sliding scale, some patients are still not able to afford the test.

Clinicians recommended an expansion of insurance coverage for the test. One clinician stated, “The insurance company policies that has stipulations on why they will pay for it and why they won't pay for it. I think personalized medicine is the best thing

yet. I know there are some inpatient facilities on the east coast that do this testing on every single patient in their facility. That's part of the intake procedure. And I think that's terrific. I think every provider should be able to gather this information at the beginning of every treatment, every course of treatment for every patient because it's actually personalized the treatment plan to that specific person."

Many clinicians found pharmacogenetic testing to be beneficial in guiding treatment decisions, however, some insurance companies will only cover pharmacogenetic testing if a person has a specific diagnosis. For example, one clinician reported that insurance companies will only cover testing if the patient is taking Plavix. While another clinician found that certain insurance companies required a diagnosis of Depression before they would cover the test. Clinicians agreed that the test provided information specific to a person's DNA not just a diagnosis or medication. Therefore, clinicians recommended an expansion of insurance coverage for persons with mental illness.

Overall, most clinicians concurred that costs should be "more clear and upfront" for the patients. One clinician stated, "I wish it would be more affordable for everybody. The price would be more reasonable, maybe in the future it could, you know."

Test Expansion

Clinicians had several recommendations including more information on old and new medications, efficacy of medications, side effects of medications, augmentation of medication, and inclusion of natural/homeopathic medications. First of all, clinicians recommended an expansion of medications listed on the report. For example, one clinician stated, "I think the company is a little slow on adding to the list of the drugs that

they test for new drugs. They are drugs that have been out for pretty good while that they don't test for and then there's a few old drugs that I use, that they don't test for. It took a long time for Trintellix. Then there's a couple that still aren't on their two and then I used some old drugs like Serzone and they don't test for that." The clinicians did not believe that the list of medications was adequate and took too long to add newer medications. Some clinicians found it time consuming when certain medications were not listed in the report. For example, a clinician reported, "you can still, mean, kind of sort of extrapolate the information because you can find out what the pharmacodynamics and pharmacokinetics and most of those drugs are and guesstimate based on the testing, although I still like to have it on the reports and not have to jump through the hoops."

Several clinicians recommended a more specific, detailed report to narrow down medication choices. One clinician stated, "I guess just, which medication would be the first one to try or which one would be, if there was any way to tell the ones that work better than one of the others that are listed as being genetically appropriate for use of the clients." Some clinicians perceived the report as being "too vague". For example, another clinician stated, "It will say here like the serum level maybe too high. Lower doses may be required. Okay, well that's fine, but you don't know if that like slightly lower dose or half the dose, I mean it's still kind of vague. Right, so maybe just more specific instead of just generally saying, yeah. Yeah, but again that might be all that they know from the science. I mean but it doesn't say anything specific, like reduce the dose at 50 percent. It might see that with somebody with renal failure or something that we have our general guidelines, but it's just kind of vague."

In addition, clinicians recommended a greater efficacy in treatment response to specific illnesses. For example, one clinician stated, “I just don’t think, I don’t think the efficacy is by any means has to, anything over 70% has been my experience.” Some clinicians found that few patients continued to have significant reactions to medications that were listed in the “green column”. For example, one clinician started a patient on Elavil and her lips began to swell. The clinician stated, “She was like, are you trying to kill me. She was really at the end of her ropes. She’s had, so much, go wrong...So, it’s still bad for...Yeah, I thought that was going to be the you know, I was going to ride in on the white horse to save the day, but I was just one more person that tried to kill her.” Clinicians stated that this has not happened often and most of the time the test is helpful. However, the clinicians reported that they would like to see some advances in the test to rule out if someone is more prone to having an allergic reaction or a significant adverse effect from the medication.

Clinicians recommended more information on medication augmentation and interactions between medications. One clinician stated, “So many of our patients don’t come in on one drug you know they all come in around six different medications with all their interactions. So, it doesn’t help me with interactions or combos you know I wish it would you know maybe that’s the next step for the gene. I wish it would show like yeah it would show okay this combination and they all come in on Wellbutrin and Zoloft.”

Additional clinicians recommended that the pharmacogenetic test included a more natural, integrative approach to treatment. One clinician stated, “I just wish that they had a way to direct us in the use of more natural things. And just, that is actually my preference is more integrative care and natural care. So, we don’t have the FDA, we got

the clinical studies or a test to tell us, which of all the over the counter products you know as a best magnesium or best millennium, or the best anything we don't have that. We do a direct patient to the National Institute of health, you know and to other places where they have some database on those things. But I wish they were a test that would tell me something like that that would be awesome.”

Additional clinicians recommend a more detailed information on specific genes. One clinician stated, “For example with the methylfolate enzymes, to have a significant size paragraph that explains what is this enzyme, and why are we testing for it, what is the difference in treatment if somebody just has a very minor error.” Some clinicians recommended a more scientific report to understand the clinical importance of the specific genes.

Overall, clinicians recommended a more detailed, specific report to look at the whole picture. Some clinicians preferred more knowledge on the integrative, natural approach to treatment including over the counter supplements. Lastly, clinicians believed the test was helpful in medication treatment decisions but the test is not “100% fool proof” at this point. Clinicians suggests that we will know more about the efficacy of the test as more people begin to use the test at a macro level.

Online Access

Several clinicians recommended online access of the report for patients and providers. For example, one clinician stated, “And I think if patients could potentially have online access to that information or easier access to that information might be more beneficial for the patients so that they could share it with the others more easily. But then again that increases access to that information from other, corporations or places that

could misuse information.” Many providers agreed that the test results would be beneficial to other healthcare providers including primary care providers, emergency providers, and pain specialists. Although many providers give a copy of the report to the patient, clinicians believed electronic access may be more beneficial.

In addition, several clinicians recommended the pharmacogenetic test results to be linked to their electronic medical records. One clinician stated, “Everything that they’re doing, that can be electronic is helpful. This is not electronically test. There’s no HL7 interface so it’s just a document, I don’t really know if it would help to have an HL7 for it, although it would be easier to handle...in terms of the medical record it might be nice to have it in the data part of the EMRs” Similarly, another clinician stated, “What would be really nice, would be, if it interfaced with the EHR. Which it doesn’t do, so that it could pull all the demographics the F codes and everything, you know, all the requirements to order the test.” Overall, clinicians believed it would be more conducive to be able to connect the report with the electronic medical records.

Patient Education

Most clinicians recommended education material for patients in “layman’s terms”. Many clinicians give a copy of the pharmacogenetic test report to the patient but feel that it is difficult for the patient to understand. One clinician recommended, “A patient education sheet or something in layman’s terms to help them understand it more when they take the copy of the report home and study it.” Similarly, another clinician stated, “I would say maybe put it in more simple terms. The reports when we give it to the patients to say like an algorithm of what treatment plan they should be on. And avoid this, stay away from this, increase this, decrease this, if you choose to use it.” Additional

clinicians recommended more educational materials for patients and a compact report for patients.

Another clinician stated, “I would like to see a clear explanation to them about what the results actually mean.” Other clinicians recommended an explanation on a brochure to provide specific details on what the test is going to show, and specify that the test does not specifically show the “most efficacious medicine or diagnosis”. Most clinicians reported that they do not have any literature about pharmacogenetic testing in their clinics to give to patients. However, clinicians did report that they believe there is some information on the website but many clinicians report they have not utilized this resource.

Many clinicians commented on the length of the pharmacogenetic testing report. One clinician stated, “But the one thing that I probably would like to see changed eventually is with the report itself it’s so lengthy. And for the patients it could be a little overwhelming if they really try to look into all the different P450 information and being are you an ultra-rapid metabolizer or slow metabolizer. You know, it comes out like 17 pages when it’s all said and done.” Most clinicians only discuss the highlights with the patient and do not discuss the different types of metabolizers.

Another recommendation by clinicians was to update the format of the report for patients. Clinicians reported the current nomenclature and format is confusing for patients. For example, one clinician stated, “One thing I don’t like about the test is it categorizes medications just kind of arbitrarily, like it will say that Prozac is an antidepressant. It only has it in on the antidepressant page. And that’s one thing Prozac is used for but its’ also used for lots of other things. It’s approved for anxiety and things

like that, the same thing for the antipsychotics. I mean they're used to augment, they're used for bipolar but they just put them on the antipsychotic page. So, if you're trying to augment an antidepressant with Abilify and the patient sees it only on the antipsychotic page, they're going to say why you giving me an antipsychotic for my depression, I'm not psychotic. You know just lump all those together because clinically when I'm going through that, I have to explain to patients. Now this is antipsychotics and you're one of these medicines and you are not psychotic. These are also medicines we use to treat...and I have to go through that spill just to remind them I'm not saying you're psychotic. I'm not saying you have schizophrenia, because I'm, you know because you're already on one of these medicines by me or from another doctor, that's not what we mean. Maybe you have irritability associated with autism maybe you have bipolar illness maybe you have to treatment resistant depression. These medicines are all used for that too not just for psychotic symptoms. So, to me I feel like that's a little bit confusing and maybe you get maybe a little bit of a negative connotation perhaps."

The same clinician also mentioned that Propranolol is listed on the test report as an anxiolytic but it is classified as a beta blocker medication. Although Propranolol is used to treat anxiety, it is also used to treat hypertension. Clinicians report this is confusing for patients when medications are used to treat more than one illness and the medication is only listed under one classification of medications on the report. Overall, clinicians would like to have more education materials available for the patient including a report that is simple for patients to understand.

Time Restraints

Many clinicians recommended a more efficient order process. Most clinicians agreed that the collection of the sample was easy and only took 30 second but the paperwork was time consuming. One clinician stated, “I can do it pretty quickly, but when people aren’t used to ordering it it’s like it’s kind of cumbersome.” Another clinician stated, wish we could do a little bit less paperwork with it, you know, the test itself takes 30 seconds and then swab 30 seconds and then paperwork takes a while, you know, this whole pile of work that needs to fill in and all that.” Similarly, another clinician stated, “the site is a little complicated we have an MA in our clinic who really struggles with trying to put in all the information and it just, you have to do things just so in order to you know order the test. So, it’s a little temperamental you know, the ordering process.” Some clinicians reported that they do not have a nurse or medical assistant to help them with the ordering process of the test which can be very time consuming. Clinicians recommended a less cumbersome process for ordering the test.

In reference to results, some clinicians recommended a quicker turnaround time to receive the results. One clinician stated, “I think it would be great to swab and who knows what the mechanism will be and instantly have the results. And you know sometimes I will say you know let’s just wait till tomorrow. And I’ll start the medication instead of let me start you off with something and then end up changing it in 24 hours if the results indicate that. So, I think it will be great if it was kind of an immediately read type of test and I think we’ll get there.” For some clinicians it can take two to three weeks to obtain results from the test which delays treatment.

Additional clinicians requested an alternative method to be able to use DNA from previous years to develop an updated report when new medications are added to the medication profile list rather than having to repeat the entire test again. One clinician stated, “But I wish if I could go back in without having to repeat the test and just have them you know run the DNA that I collected a few years ago with the new testing. That would be really convenient rather than if I, you know, if I wanted to do test for mood stabilizers. Then I have to have the patient come back in do the whole procedure again, versus, just adding a test on the sample that we've already submitted that would be really nice.”

Overall, clinicians recommended less paperwork and a more efficient way to order the test. In addition, clinicians desired a more rapid turnaround time for test results so that treatment could be initiated sooner. Lastly, clinicians recommended an updated report when new medications are added to the medication profile without repeating the entire test.

Policy Concerns and Challenges

In regards to pharmacogenetic testing, several policy concerns and challenges are evident and should not be overlooked. Several challenges with insurance coverage were identified. These challenges included restrictions on pharmacogenetic testing and medication coverages. Another challenge identified was the lack of formal education for clinicians regarding pharmacogenetic testing. This section discussed the impact of these challenges on pharmacogenetic testing in clinical practice.

Insurance coverage

Many clinicians reported significant policy concerns with insurance coverage for pharmacogenetic testing and medication coverage. Clinicians reported that insurance companies put restrictions on specific diagnostic codes and would only cover testing for persons with a specific diagnosis. In addition, clinicians have found that insurance plans require them to prescribe first line medications despite the pharmacogenetic testing results.

For example, one clinician reported that it would not be useful to conduct the test on a medication naïve patient if the insurance will require them to try a certain medication first. This clinician stated, “The first-line treatments that their Medicaid plan covers, we still have to start with trying them.” Clinicians found that medication coverage by insurance companies was not influenced by the results of the pharmacogenetic testing.

Many clinicians found that some of the brand medications or off-label use medications suggested by the pharmacogenetic testing were not covered by insurance plans. Insurance plans either required a generic medication as first-line or a recorded number of failed trials before they would cover a medication that might be suggested by the test. For example, clinicians reported that the patient may be a normal metabolizer for a newer medication that the insurance company will not cover although the insurance company paid for the pharmacogenetic testing. In addition, some insurance companies may not cover medications that are off-label uses such as Pristiq or Lamictal in children.

These policy concerns were significant barriers for clinicians. Many clinicians believed that if the test results revealed that a person would benefit from a non-formulary medication, then insurance should take this into consideration when providing medication

coverage. In addition, clinicians professed that insurance companies should expand pharmacogenetic testing coverage beyond one specific diagnostic code or diagnosis.

Formal Education for Clinicians

Most clinicians reported that they did not receive any formal training on pharmacogenetic testing. In this sample, the majority of clinicians received training from pharmacogenetic testing representatives. Clinicians reported that the training consisted mostly of how to obtain the DNA sample and order the test. The clinicians stated that the pharmacogenetic testing companies provided resources for providers including geneticists and Pharm D's who are available by phone to answer any questions about the test and how it works. However, many clinicians in this sample reported that they have not utilized these resources.

Some clinicians learned about pharmacogenetic testing from peers and by seeking training on their own through training institutions and online research on the topic. Clinicians in the sample found additional educational courses on pharmacogenetic testing at the University of Colorado, Stanford University, and the Clinical Pharmacogenomics Implementation Consortium. Few clinicians in the sample learned about pharmacogenetic testing during graduate school. One clinician stated, "It's not in either clinical track curricula, nor is it in MD curricula or PA. You know, people know that it exists, but they don't know what it means. Like just because things are on my panel, it does not necessarily mean that the evidence is there for it to be clinical actionable. But of course, if you listen to the vendor, they will tell you, oh absolutely it is. But the reality is that the evidence they say not quite be there yet. It certainly wasn't taught to me in school, in my university, it absolutely should have been." Similarly, another clinician stated, "you

know the pathways, the Cytochrome P450 pathways, I don't even hardly even understand that. You know I mean I get what that means but I mean outside of any confusion, or concerns, or anything about that how I'm interpreting except I'll even call pharmacists who I have that my personal contact or I call the or just call the number that's on the gene test thing there is the number on the results of the test that you can call to talk to a Pharm D and talk to them about how to interpret the test or apply the information of the test.”

Overall, there is a need for extensive and formal educational training for clinicians who are utilizing pharmacogenetic testing in clinical practice. While some clinicians in the sample have a broader understanding of pharmacogenetic testing, other clinicians believe that their knowledge is limited. The implementation of pharmacogenetic training in nursing and medical curricula may benefit future clinicians who will be utilizing pharmacogenetic testing in clinical practice.

Chapter V

INTERPRETATIONS, CONCLUSIONS, AND RECOMMENDATION

This study's aim was to evaluate mental health clinicians' perceived knowledge regarding pharmacogenetic testing, their attitude, receptivity towards, and confidence in pharmacogenetic testing, and how pharmacogenetic testing is being implemented in outpatient mental health clinics. This study compared experiences of 28 mental health clinicians regarding experience with pharmacogenetic testing. The relevant themes of this qualitative descriptive analysis focused on the perceptions of pharmacogenetic testing, impact on clinical decision-making, associated concerns of pharmacogenetic testing, knowledge gaps among clinicians, and policy challenges. This chapter discusses the summary of findings, implications for research, practice and policy, unique attributes of the study, and limitations of the study.

Summary of Findings

Clinicians in this study have been using pharmacogenetic testing from two months to twelve years in outpatient mental health clinics to guide treatment decisions. Many of the participants utilized pharmacogenetic testing to guide dosing and medication selection to decrease the risk of side effects and increase tolerability of psychotropic medications. Clinicians found that patients are receptive to pharmacogenetic testing and have an overall good understanding of the test. Despite the receptivity and benefits of pharmacogenetic testing, clinicians have received minimal formal training on such testing in clinical practice. However, clinicians continue to use the test and have positive results. Some clinicians stated that the test is not "100% fool proof" but they have found it

helpful in the majority of cases. Clinicians identified some downsides and risks of the test, as well as, some recommendations to improve the practicability of the test.

A Tool for Prescribing

Clinician's views about pharmacogenetic testing were similar to previous studies that discussed how to implement pharmacogenetic testing in clinical practice (Dunbar et al., 2012; Walden, et al. 2015). Pharmacogenetic testing was viewed as an additional tool to assist with medication selection and dosing of medications. In contrast to previous studies, clinicians in this sample obtained the DNA sample using a buccal swab or saliva specimen, whereas, previous studies obtained a blood sample, (Dunbar et al., 2012; Walden et al., 2015). Clinicians in this study utilized a variety of pharmacogenetic testing companies including: Genesight, Genomind, Millennium, Ingenetics, Ventari, and IDgenetics. Most clinicians chose a company based on input from colleagues and recommended choosing a testing company with a good reputation and evidence based literature.

Initial Exposure and Training

Clinician's exposure to pharmacogenetic testing was very limited. Most clinicians in this study initially learned about pharmacogenetic testing through testing company representatives and colleagues. In contrast, previous literature suggests that the primary source of education for psychiatrists was attending a continuing education course or reviewing the current medical literature. However, many clinicians in this sample reported that no formal education was provided. Similarly, to previous literature, few clinicians learned about pharmacogenetic testing their training programs of study. Hoop et al. (2010) found that 61% of psychiatry faculty and residents (n=67) received none to

minimal training on pharmacogenetic testing. Some clinicians in this sample sought additional training at conferences and seminars through educational institutions.

Factors Considered in Decision-Making

Clinicians identified cost as a major factor in deciding to order pharmacogenetic testing for patients with mental illness. Although most government payers cover the cost of the test, many patients with commercial insurance or no insurance could not afford the test. Clinicians in this sample were less likely to order pharmacogenetic testing for patients with commercial insurance or cash payers. Similarly, previous literature concurred that the cost of the test was a potential disadvantage of pharmacogenetic testing (Dunbar et al., 2012).

Another factor in decision-making identified by clinicians included the benefits of the test. Clinicians in this sample found the test lessened patient's fears and anxieties about medications, validated patient's experiences, and improved tolerability and adherence of medications. Similarly, additional researchers found that mental health clinicians believed pharmacogenetic testing improved trust and rapport with patients and clinicians, improved medication adherence, and predicted fewer side effects from medications (Dunbar et al., 2012).

Another major deciding factor that influenced clinicians to order the test included if the patient was medication naïve or had experienced multiple medication failures. Most clinicians in this sample were more likely to order pharmacogenetic testing for patients who had multiple medication failures or adverse effects from medications. Similarly, mental health clinicians in previous studies perceived the test to be useful in patients who

may have an increased sensitivity to medications to improve medication tolerance (Dunbar et al., 2012; Hoop et al., 2010).

The severity of illness was a significant factor in decision-making for ordering pharmacogenetic testing. Clinicians were more likely to order testing in patients with more severe or treatment resistant mental illness. Most clinicians were not likely to order pharmacogenetic testing for patients who were stable and doing well on their current medication regimen.

Impact on Clinical Decision-Making

The impact of pharmacogenetic testing on clinical decision-making matches with several studies that discuss the perceived usefulness of pharmacogenetic testing.

Clinicians in this study found that pharmacogenetic testing provided reassurance to the clinician and patient. Clinicians believed that the test often provided confirmation that they were “on the right track”. Similarly, a previous study found that mental health clinicians perceived pharmacogenetic testing confirmed prior clinical decisions and judgement regarding medication dosing and clinicians (Dunbar et al., 2012). In addition, clinicians were more confident in their decisions (Dunbar et al., 2012). Clinicians found that pharmacogenetic guided treatment gave them permission to go beyond their normal choice of treatment in certain situations especially in the adolescent population.

Clinicians in this study found pharmacogenetic testing to be influential in understanding how the metabolizing of medications can impact patients who have been resistant to treatment. Similarly, previous researchers found that mental health clinicians found pharmacogenetic testing to be effective in patients who were “abnormal metabolizers” of medications and at risk of adverse effects of medications even at lower

doses (Dunbar et al, 2012). Clinicians in this sample found pharmacogenetic testing to reduce trial and error and provides a more scientific approach to treating patients with mental illness.

Although the majority of clinicians found the test to have a positive impact on clinical decision-making, approximately 25% of participants believed the pharmacogenetic guided treatment did not have a significant impact on clinical decision-making. Clinicians found that results may indicate that the patient does not have any metabolism abnormalities with medication or the medication indicated is not clinically relevant to the patient's symptoms. Clinicians perceived that the test was not "100% fool proof". Some clinicians believed that the test was accurate 90% of the time while others believed it was accurate only 50% of the time.

Shared Decision-Making

Shared decision-making was defined by clinicians as open dialogue with the patient and clinician and giving patient treatment options along with the clinician's clinical judgement. Most clinicians practiced this model of care with or without the pharmacogenetic guided treatment. Correspondingly, to previous literature, clinicians believed that shared decision-making and pharmacogenetic guided treatment built a level of trust and rapport with patients (Dunbar et al., 2012).

Populations Who Do Not Benefit from Pharmacogenetic Testing

Several populations were identified in the study that clinicians perceived would not benefit from pharmacogenetic testing. Clinicians believed that patients who were currently stable on medications, medication naïve, preferred alternative treatment, or had cognitive distortions or a personality disorder would have limited benefits from

pharmacogenetic testing. Previous research is limited in this area, however, psychiatry faculty and residents believed that pharmacogenetic testing should only be tested on patients with clinical decision-making capacity (Hoop et al., 2010).

Risks and Downsides

Clinicians acknowledged several risks or downsides to pharmacogenetic testing. A major risk or downside for some clinicians was a lack of clinical evidence for patients who have other mental illnesses besides depression. Researchers have found pharmacogenetic testing to demonstrate clinical effectiveness as a guide to medication selection in two open-label cohort studies and one randomized, double-blind controlled trial (Hall-Flavin et al., 2012; Hall-Flavin et al., 2013; Winner et al., 2013). In all three studies, participants who received pharmacogenetic testing experienced a greater improvement in depressive symptoms when compared to the unguided group (Hall-Flavin et al., 2012; Hall-Flavin et al., 2013; Winner, Carhart, Altar, Allen, & Dechairo, 2013). Further research is needed to explore the impact of pharmacogenetic testing on clinical outcomes in other patient populations since these studies are limited to patients with depressive symptoms only.

Another downside acknowledged by clinicians was whether the test reports were too simplistic or too scientific. Some clinicians preferred a more detailed scientific report while others preferred a simplified “genetics for dummies” report. Some clinicians prefer to look at a summary of the genes whereas, other clinicians prefer to look at the “green, yellow, red” columns in the report to determine medication selection.

Medication and cost barriers were recognized as major downsides by clinicians. Many clinicians found that insurance would not cover off-label medications, medical

foods such as Deplin or L-methylfolate, or some brand name medications even if the medications are indicated clinically and by the pharmacogenetic test results. Another major downside was the cost of the test. Clinicians found that government payers cover the cost of the test 100%, however, commercial payers and cash payers may not be able to afford the test. Some testing companies provide an income-based sliding scale, but clinicians are concerned that some patients may not be able to afford the sliding scale rates. In addition, clinicians reported that some patients are receiving an “explanation of benefits” and interpret this as a bill causing undue stress on the patient.

Lastly, some clinicians are concerned about the misinterpretation or misuse of the data obtained from the test. Clinicians believe there is a risk of patients or clinicians misinterpreting the test results. In addition, there are some ethical concerns such as DNA being misused by insurance companies or a patient may internalize the results negatively. Similarly, psychiatry faculty and residents believed that pharmacogenetic testing could potentially cause a patient psychological distress (Dunbar et al., 2012).

Patient’s Perception of Pharmacogenetic Testing

The majority of clinicians in this sample perceived patient “buy in”, perceived effectiveness, and patient education to be significant factors in the patient’s perception of pharmacogenetic testing. Many clinicians believed that the patient’s level of understanding was greatly affected by how the provider educates the patient. Clinicians reported spending up to one hour discussing the test and results. Most clinicians recommended providing a simple explanation of results depending on the patient’s education level.

Overall, patients were receptive of the test. Clinicians found the test provided hope, trust, and confidence among patients. The patients were favorable to having something that is on paper and more scientific than the traditional trial and error approach. Clinicians also believed that patient “buy in” was a significant factor in clinical outcomes. Some clinicians perceived that the test had a “placebo effect” which may improve clinical outcomes.

Application of Test Results Among Clinicians

Pharmacogenetic testing is not unique to this study, but other researchers have shown the perceived usefulness of such testing in among patients with mental illness. Previous researchers have focused on the impact of pharmacogenetic testing among patients with depressive disorders but limited studies exist on clinical outcomes of other psychiatric disorders. Clinicians in this sample found the test applicable to several different patient populations including Adolescents, Autism and Non-verbal patients, Addiction Disorders, ADHD, Anxiety Disorders, Depressive Disorders, and Schizophrenia. Clinicians found pharmacogenetic testing to be helpful to reduce side effects and improve medication tolerability among these patients. Additional studies are needed to further explore clinical outcomes in these patient populations.

Clinician Recommendations

Clinicians recommended test affordability, test expansion, online access of results, patient education materials, and more efficient ordering process of pharmacogenetic testing. Overall, clinicians concurred that the cost of pharmacogenetic testing should be more affordable to patients. Clinicians also recommended expanding the test to include more of the older and newer medications, along with more details

about interactions among drug combinations used in clinical practice. Some clinicians requested an integration of natural/homeopathic medications into the report. Several clinicians recommended linking the report with electronic medical records.

Another major concern for several clinicians was the format and nomenclature of the report. Most clinicians preferred more educational materials for patients that explains the results in “layman’s terms”. Many clinicians believe the report is confusing for patients and difficult for them to understand.

Lastly, clinicians recommended a more efficient ordering process and faster turnaround time for results. Similarly, previous researchers found that psychiatry faculty and residents also experienced delays in testing results and staff had poor accessibility in test forms (Dunbar et al., 2012). On average, clinicians received test results within two to three weeks, however, some clinicians received results as soon as forty-eight hours. In addition, clinicians found the ordering process to be tedious and time consuming.

Policy Concerns and Challenges

A major policy concern and challenge identified by clinicians was insurance coverage for the test and medications. Clinicians reported restrictions from insurance companies that only provided coverage for pharmacogenetic testing for specific diagnostic codes. Although insurance companies paid for the pharmacogenetic test, clinicians reported that insurance plans would only cover medications on their formulary despite findings on the pharmacogenetic test.

Another significant policy concern and challenge among clinicians was the lack of formal education for clinicians. Most clinicians have not received formal training on pharmacogenetics but have learned from pharmacogenetic testing representative and

colleagues. There is a need to implement pharmacogenetic education in medical and nursing curricula along with expanding continuing education options for clinicians.

Implications for Practice

Pharmacogenetic testing can be useful for the mental health clinician in understanding and avoiding drug-drug interactions when prescribing medications (Kung & Xiaofan, 2010). A person's metabolizer status can determine the pathway medications are metabolized to determine dosage and reduce the medication combinations used in the treatment of mental illness. Pharmacogenetic testing can prevent unnecessary, ineffective treatment (Cascorbi & Tyndale, 2014). The clinical implications of this study are: 1) To enhance other clinicians' level of confidence and acceptance regarding pharmacogenetic testing in clinical practice, 2) Assist mental health clinicians to determine the type of patients that may benefit from pharmacogenetic testing, 3) Inform clinicians how pharmacogenetic testing is being used in clinical decision-making regarding medication management, and 4) Increase clinicians' knowledge of how pharmacogenetic is being used to educate families and patients.

Confidence and Acceptance of Pharmacogenetic Testing

Previous research confirms that the majority of clinicians welcome pharmacogenetic testing and believe that patients would benefit from such testing (Thompson, Hamilton, & Hippman, 2015). However, the implementation of pharmacogenetic in mental health has been sluggish despite the support of pharmacogenetic testing in the literature (Burke, Love, Jones, & Fife, 2016). Burke et al., (2016) suggests that some clinicians may be unaware that such testing is available or unaware of the applicability of pharmacogenetic testing among patients with mental

illness (Squassina et al., 2010). However, patients expect clinicians to be knowledgeable about pharmacogenetic testing (Squassina et al., 2010). This study can be used to inform other mental health clinicians about the usefulness of pharmacogenetic testing which may increase clinicians' knowledge level and confidence level, therefore, increasing the number of clinicians using such testing in mental health practice. Focusing on the clinicians' experience with pharmacogenetic testing will provide a unique opportunity for the results to be understood by other clinicians which is pertinent to the acceptance of the intervention (Sullivan-Bolyai et al., 2005).

Identify Target Populations

This study will help clinicians identify the type of patients who may benefit from pharmacogenetic testing in clinical practice. Although pharmacogenetic testing provides gene-drug information for various psychotropic medications, most studies have been focused on adults with depression (Hall-Flavin et al., 2012; Hall-Flavin, et al., 2013; Winner, Carhart, Altar, Allen, & Dechairo, 2013). However, these tests are being used to guide treatment in patients with anxiety, schizophrenia, mood disorders, and other mental illnesses in clinics. This study provides clinicians with information on who is being tested and the perceptions of clinician's regarding what population may or may not benefit from such testing. This will help the clinician identify target populations in their clinical setting.

Medication Planning and Monitoring

Traditional treatment for patients with mental illness has focused on a trial and error approach to prescribing medications (Langman & Dasgupta, 2012). A trial and error approach increase the risk of side effects, being over medicated, or the medication being

ineffective to treat symptoms (Mrazek, 2010). In pharmacogenetic testing, genetic factors are being used by clinicians to guide medication selection and dosing of medication to improve patient outcomes (National Institutes of Health: National Human Genome Research Institute, 2014).

Researchers have found that a patient's metabolizer status can be determined according to certain enzymes (Black, O'Kane, & Mrazek, 2007). Patients may be ultra-rapid metabolizers (greater ability to metabolize medications), extensive metabolizers (normal ability to metabolize medications), intermediate metabolizers (less ability to metabolize medications), or poor metabolizers (no ability to metabolize medications) of a certain medication – requiring very different doses or perhaps different medications-- depending on their genetic expression of a particular enzyme (Black et al., 2007). For example, patients identified as poor metabolizers are at increased for side effects, while an ultra-rapid metabolizer is unlikely to respond to standard doses of medications. Pharmacogenetic testing guided treatment can improve the accuracy of medication responses and decrease the risk of side effects (Mrazek, 2010). Researchers found that ultra-rapid metabolizers had multiple medication failures and untreated symptoms and were at greater risk of completed suicide than those who died from natural causes (Zackrisson, Lindblom, & Ahlner, 2010).

This study provides clinicians with information on how mental health clinicians are using pharmacogenetic testing to guide medication selection and monitor among patients with mental illness. A greater understanding of how to use pharmacogenetic testing in medication management may reduce polypharmacy which is common in mental health prescribing (Laje, 2013). Since there are no current guidelines, understanding the

clinicians' decision-making process guided by pharmacogenetic testing can be valuable for clinicians to adapt these findings into clinical practice.

Patient and Family Education

This study may help clinicians translate pharmacogenetic testing into practice by understand how clinicians are using pharmacogenetic testing to educate patients and families regarding their treatment plan. This information can be beneficial to clinicians who are beginning to implement pharmacogenetic testing in practice. Often patients do not understand medical terminology and clinicians are responsible for promoting patient understanding of pharmacogenetic testing results (Haga, Mills, & Bosworth, 2014). Terms such as “ultra-rapid metabolizer” may be confusing to a patient or family member and lead to unwarranted anxiety (Haga et al., 2014). In addition, understanding how clinicians are communicating test results may assist in the development of educational aids for patients and families regarding pharmacogenetic testing.

Implications for Policy

Currently, there are no clinical guidelines using pharmacogenetic testing in mental health practice (Quinones et al., 2014). However, a large majority of clinicians believe that pharmacogenetic testing will become the standard of care (Walden et al., 2015). The study provides insight on clinicians' deciding factors when determining who receives treatment, as well as, how the test is interpreted and applied in the clinical setting. This information may provide a foundation for developing pharmacogenetic testing guidelines and policy in mental health clinical practice.

In addition, this study provides a foundation for educational programs for clinicians using pharmacogenetic testing. Research consistently shows clinicians

typically report limited knowledge or understanding of pharmacogenetic testing (Dodson, 2011). This study explores clinicians' knowledge base regarding pharmacogenetic testing and provides insight regarding gaps in clinicians' knowledge. This information can help guide curriculum development on pharmacogenetics in medical and nursing programs. In addition, the information can be used to develop continuing education programs for current clinicians to learn about the implications of pharmacogenetic testing in clinical practice.

Lastly, this study provides information for payers regarding insurance coverage for pharmacogenetic testing and medication coverage. Clinicians reported inconsistencies among payers and medication coverage. For example, payers who provide coverage for pharmacogenetic testing continue to have limited coverage for non-formulary medications despite testing results. In addition, some payers have limited coverage for pharmacogenetic testing to specific diagnostic codes which may not be applicable to all patients who would benefit from pharmacogenetic testing.

Implications for Research

Further research is needed to explore patient outcomes from pharmacogenetic testing interventions (Fackler & McGuire, 2009). This study provides a foundation for future studies on the impact of pharmacogenetic testing on medication adherence and tolerability, medication efficacy, and shared decision-making. Additional studies are needed to explore the implementation of pharmacogenetic testing and patient outcomes in mental health clinics (Burke et al., 2016).

Medication Adherence and Tolerability

The tolerability and effectiveness of psychotropic medications is highly variable. Approximately 60% of patients do not respond completely to antidepressants and 30% do not respond at all (Crisafulli, Fabbri, Porcelli, Drago, SPina, & Deronchi, 2011). Similarly, 74% of patients being treated for Schizophrenia discontinued medications due to side effects and ineffectiveness (Lieberman, Stroup, McEvoy, Swartz, Rosenheck, Perkins, & Hsiao, 2005). Due to genetic factors, patients may vary widely in how they respond to mental health medications. For example, genetic factors contribute to approximately 50% of antidepressant responses (Crissafull et al., 2011). Patients metabolize antidepressants at vastly different rates and can experience different responses to the same drug (Dalen, Dahl, Ruiz, Nordin, & Bertilsson, 1998; Lohaff & Ferraro, 2010).

This study provides a foundation for future studies to determine if pharmacogenetic guided treatment may be a key factor in medication adherence and tolerability. Researchers found that pharmacogenetic guided treatment improved depressive symptoms among adult patients with depression (Hall-Flavin et al., 2012; Hall-Flavin, et al., 2013; Winner et al., 2013). In a retrospective study, researchers found patients who received pharmacogenetic guided treatment were significantly more adherent to medications when compared to the standard treatment group (Fagerness et al., 2014). Limited studies have been conducted on the effects of pharmacogenetic guided treatment on medication adherence among patients with mental illness.

Medication Efficacy

Patients who are characterized as rapid ultra-metabolizer are at the greatest risk for experiencing reduced efficacy in medications (Mrazek, 2010). Future research is needed to assess effects of pharmacogenetic testing on medication efficacy among patients with mental illness. Previous studies have focused primarily on patients with depression. In two open label cohort studies and one randomized controlled trial, participants who received pharmacogenetic guided treatment had improvement in depressive symptoms when compared to the standard treatment group (Hall-Flavin et al., 2012; Hall-Flavin, et al., 2013; Winner et al., 2013). Additional randomized controlled trials are needed to further explore medication efficacy among patients with mental illness. This study provides a foundation for exploring patient outcomes related to pharmacogenetic guided treatment and medication efficacy.

Shared Decision-Making

Historically, the primary approach to decision making was a paternalistic approach where providers assumed the dominant role in treatment decisions by making a decision based on clinical findings and scientific evidence (Charles et al., 1999). Researchers have found that most patients with mental illness want to be involved in decision making regarding their treatment including medications and hospitalizations (Hamann, Cohen, Leucht, Busch, & Kissling, 2005). Pharmacogenetic testing is one way clinicians can implement shared decision-making among patients with mental illness in the selection of medications and adherence medications.

Previous research has focused on exploring clinician and patient views on shared-decision making or patient outcomes (Patel, Schnall, Little, Lewis-Fernandez, & Pincus,

2013; Stevenson, Barry, Britten, Barber, & Bradley, 2000). Researchers have found shared decision-making to be effective in improving medication adherence, greater patient satisfaction with care, and improvement in psychiatric symptoms among patients with mental illness (Hamann et al., 2006; Loh et al., 2007, Van Korf et al., 2003; Van Os et al., 2004). However, to the author's knowledge, no studies have been conducted on how pharmacogenetic guided treatment has been integrated into shared decision-making. This study explored how clinicians are implementing shared decision-making in treatment decision using pharmacogenetic guided treatment. This study provides a foundation for future studies on shared decision-making in this population.

Unique Attributes of the Study

This qualitative descriptive study evaluated mental health clinicians' perceived knowledge regarding pharmacogenetic testing, their attitude, receptivity towards, and confidence in pharmacogenetic testing, and how pharmacogenetic testing is being implemented to support precision medicine in outpatient clinics. Few studies have examined clinicians' knowledge and perceptions of pharmacogenetic testing or how such testing is being implemented into clinical practice. In addition, previous studies have focused primarily on psychiatrists, psychiatrist residents, and undergraduate medicine students. This study includes Advanced Practice Nurses (Nurse Practitioners and Clinical Nurse Specialists), Medical Doctors (Psychiatrists), and Physician Assistants who are utilizing pharmacogenetic testing in outpatient mental health clinics. Advanced Practice Nurses are at the forefront of patient care and can evaluate genetic factors associated with medication dosing and tolerability (Davies, Conley, & Puskar, 2010). In addition, this study focused on how clinicians are actively implementing pharmacogenetic testing in

practice. Previous studies have primarily focused on healthcare professionals with limited or no experience with pharmacogenetic testing (Walden et al., 2015). Lastly, the timing of this study, during a time when pharmacogenetic testing is becoming more prevalent, may have captured some unique characteristics of how to implement such testing in clinical practice, as well as, provide a foundation to develop clinical guidelines for pharmacogenetic testing.

Limitations

Several important limitations emerged from this study. First of all, the generalizability of study findings may be limited by the study population primarily from the Southeast region (SC, NC, and GA; n=21) of the United States; however other participants were from a variety of locations across the United States including AZ, MO, MN, OR, IN, and HI. Future studies are needed to use a more diverse sample of clinicians including clinical psychologists and other mental health prescribing clinicians. The sample in this study consisted of Nurse Practitioners, Clinical Nurse Specialists, Psychiatrists, and Physician Assistants. In addition, this study focused on mental health clinicians working in outpatient mental health clinics. Future studies may need to include clinicians at inpatient and residential mental health facilities. Lastly, the sample size in this study was limited to twenty-eight mental health clinicians. Sampling in qualitative research can be challenging since the access population may not represent the full target population and sample sizes may be significantly smaller (Polit & Beck, 2016).

Despite these limitations, this study has clinical significance. Few research studies have examined clinicians' knowledge, perception, and implementation of pharmacogenetic testing in mental health clinics. Previous studies have focused on

healthcare professionals with limited or no experience with pharmacogenetic testing or academic centers (Hoop et al., 2010; Walden et al., 2015). Most importantly, this study will lead to future research to support shared decision-making around pharmacogenetic testing, medication adherence and tolerability, and setting guidelines for pharmacogenetic testing in mental health clinics. Findings from this study, in conjunction with future studies, will provide the foundation to develop clinical guidelines for pharmacogenetic testing and the implementation of pharmacogenetic testing into medical and nursing curriculum.

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**Appendix A
Demographic Form**

1. What is your Professional Title?

- M.D. or D.O.
- Nurse Practitioner
- Clinical Nurse Specialist
- Clinical Psychologist
- Physician Assistant
- Other _____

2. What is your current age? _____

3. What is your gender? ____ Male ____ Female

4. How long have you been practicing as a mental health clinician?

_____Months _____Years

5. How long have you been using pharmacogenetic testing in clinical practice?

_____Months _____Years

6. What type of pharmacogenetic test are you using in clinical practice?

7. What is the approximate number of patients who receive pharmacogenetic testing in your

clinical practice? _____

8. What is the average number of patients that see in your practice per month?

Appendix B

Semi-structured Interview Guide

Clinician: Can you tell me about your experiences with pharmacogenetics testing?
Follow up questions/probes as needed:

- How does the test work? How did you first learn about this type of test?
- What kind of training, if any, have you had that prepared you to use this kind of test in practice? How did you decide to use, or not use pharmacogenetics testing in your practice?
- Has pharmacogenetics testing changed your practice? If so, how?
- Who does the test benefit? How has the test been beneficial?
- How often are you using pharmacogenetics testing with your patients?
- How do you think your patients perceive pharmacogenetics testing? How well do you think patients understand the test?
- How do you decide who will receive pharmacogenetics testing? When do you introduce it into your clinical workflow?
- How do you include shared decision-making when making clinical decisions guided by the pharmacogenetics testing?
- What type of patients who would not benefit from this test? What patients would you not recommend it for?
- Are there risks to pharmacogenetics testing? Downsides? Do you have concerns about this practice?
- If you could change anything about the test, what would you change?
- Any other questions I should have asked you?

VITA

Tammie Gainey was born on March, 15, 1979 in Wytheville, Virginia. She has one younger sister who lives in Thailand and two step sisters who live in North Carolina. Her family relocated to Concord, North Carolina and she graduated from Central Cabarrus High School in Concord, North Carolina in 1997. She obtained her Bachelor of Science in Nursing from the University of North Carolina at Charlotte in 2001. Her clinical experience was primarily Adult Intensive Care and Cardiovascular nursing. In 2004, she graduated from Kennesaw State University with a Master of Science in Nursing degree with a specialty as a Family Nurse Practitioner. She completed a Post-Master's Certificate at the University of South Carolina with a specialty as a Psychiatric Mental Health Nurse Practitioner in 2017. She decided to pursue her doctoral degree at the University of Missouri Sinclair School of Nursing in 2013. Her dissertation research was successfully funded by the *Midwest Nursing Research Society Joseph and Jean Buckwalter Grant*. She currently resides in North Carolina with her husband and three sons, Joshua, Jason, and Jaron.